Clinical trial results:
A Phase 3, Randomized Study of Adjuvant Immunotherapy with Nivolumab Combined with Ipilimumab Versus Nivolumab Monotherapy after Complete Resection of Stage IIIb/c/d or Stage IV Melanoma (CheckMate 915: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 915)

Summary

EudraCT number	2016-003729-41
Trial protocol	AT DE CZ BE ES GB PL FR GR IT Outside EU/EEA RO
Global end of trial date	02 February 2021

Results information

Result version number	v1 (current)
This version publication date	12 August 2021
First version publication date	12 August 2021

Trial information

Trial identification

Sponsor protocol code	CA209-915

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	Chaussée 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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000117-PIP02-10, EMEA-001407-PIP01-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 March 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy, as measured by recurrence-free survival (RFS), provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV no evidence of disease (NED) melanoma (in all randomized participants with PD-L1 expression level < 1%. and all randomized participants)

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	11 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 302
Country: Number of subjects enrolled	Austria: 24
Country: Number of subjects enrolled	Belgium: 38
Country: Number of subjects enrolled	Brazil: 52
Country: Number of subjects enrolled	Canada: 102
Country: Number of subjects enrolled	Czechia: 45
Country: Number of subjects enrolled	France: 202
Country: Number of subjects enrolled	Germany: 214
Country: Number of subjects enrolled	Greece: 45
Country: Number of subjects enrolled	Israel: 45
Country: Number of subjects enrolled	Italy: 216
Country: Number of subjects enrolled	New Zealand: 19
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Romania: 53
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Spain: 139
Country: Number of subjects enrolled	Switzerland: 40
Country: Number of subjects enrolled	United Kingdom: 89
Country: Number of subjects enrolled	United States: 176

Worldwide total number of subjects	1844
EEA total number of subjects	1007

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)	3
Adults (18-64 years)	1333
From 65 to 84 years	504
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1844 participants randomized and 1833 treated. Reasons not treated: 1 disease progression; 2 participants withdrew consent; 1 poor/non-compliance; 4 participants no longer met study criteria; 3 not reported

Period 1

Period 1 title	Pre-treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivo + Ipi

Arm description:

Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)

Arm type	Experimental
Investigational medicinal product name	BMS-936558 Nivolumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg IV Q2W

Investigational medicinal product name	Ipilimumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/Kg IV Q6W

Arm title	Arm B: Nivo

Arm description:

Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49

Arm type	Experimental
Investigational medicinal product name	BMS-936558 Nivolumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg IV Q2W

Number of subjects in period 1	Arm A: Nivo + Ipi	Arm B: Nivo
Started	920	924
Completed	916	917
Not completed	4	7
Disease progression	-	1
Participant withdrew consent	1	1
Not reported	2	1
Participant no longer meets study criteria	1	3
Poor/non-compliance	-	1

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A: Nivo + Ipi

Arm description:

Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)

Arm type	Experimental
Investigational medicinal product name	Ipilimumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/Kg IV Q6W

Investigational medicinal product name	BMS-936558 Nivolumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg IV Q2W

Arm title	Arm B: Nivo

Arm description:

Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on

Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49

Arm type	Experimental
Investigational medicinal product name	BMS-936558 Nivolumab Solution for Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg IV Q2W

Number of subjects in period 2	Arm A: Nivo + Ipi	Arm B: Nivo
Started	916	917
Completed	364	561
Not completed	552	356
Disease progression	166	208
Adverse Event unrelated to study drug	15	7
Participant withdrew consent	5	10
Study drug toxicity	317	104
Participant no longer meets study criteria	1	3
Other reasons	12	4
Participant request to stop therapy	33	20
Poor/non-compliance	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)	
Reporting group title	Arm B: Nivo
Reporting group description:	
Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49	

Reporting group values	Arm A: Nivo + Ipi	Arm B: Nivo	Total
Number of subjects	920	924	1844
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	3	3
Adults (18-64 years)	662	671	1333
From 65-84 years	257	247	504
85 years and over	1	3	4
Age Continuous			
Units: Years			
arithmetic mean	53.8	54.6	
standard deviation	± 14.6	± 13.7	-
Sex: Female, Male			
Units: Participants			
Female	405	387	792
Male	515	537	1052
Race/Ethnicity, Customized			
Units: Subjects			
White	907	911	1818
Black or African American	4	1	5
American Indian or Alaska Native	0	1	1
Asian	3	5	8
Other	6	6	12
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	22	22	44
Not Hispanic or Latino	359	376	735
Unknown or Not Reported	539	526	1065

End points

End points reporting groups

Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)	
Reporting group title	Arm B: Nivo
Reporting group description:	
Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49	
Reporting group title	Arm A: Nivo + Ipi
Reporting group description:	
Arm A: nivolumab 240 mg IV Q2 weeks plus ipilimumab 1 mg/kg IV Q6 weeks (for 1 year of study drug treatment)	
Reporting group title	Arm B: Nivo
Reporting group description:	
Arm B: nivolumab 480 mg IV Q4 weeks (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49	

Primary: Recurrence-free Survival (RFS) - all randomized participants

End point title	Recurrence-free Survival (RFS) - all randomized participants
End point description:	
RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma (including melanoma in situ), or death (from any cause), whichever occurred first. Median values based on Kaplan-Meier Estimates.	
End point type	Primary
End point timeframe:	
From randomization to Study Completion Date (up to approximately 45 months)	

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	922		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio RFS - all randomized
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo

Number of subjects included in analysis	1840
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.04

Primary: Recurrence-free Survival (RFS) - all randomized participants with PD-L1 expression level < 1%

End point title	Recurrence-free Survival (RFS) - all randomized participants with PD-L1 expression level < 1%

End point description:

RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma (including melanoma in situ), or death (from any cause), whichever occurred first. Median based on Kaplan-Meier Estimates. PD-L1 expression levels based on Interactive Response Technology (IRT).

End point type	Primary

End point timeframe:

From randomization to Study Completion Date (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	350		
Units: Months				
median (confidence interval 95%)	33.15 (22.21 to 99999)	27.63 (19.81 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio RFS - all randomized with PD-L1 <1%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	697
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.14

Secondary: Overall Survival (OS) - all randomized participants	
End point title	Overall Survival (OS) - all randomized participants
End point description:	
OS is defined as the time between the date of randomization and the date of death. Median based on Kaplan-Meier Estimates.	
End point type	Secondary
End point timeframe:	
From randomization to date of death (up to approximately 45 months)	

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	918	922		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio OS - all randomized
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	1840
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.32

Secondary: Overall Survival (OS) - all randomized participants with PD-L1 expression level < 1%	
End point title	Overall Survival (OS) - all randomized participants with PD-L1 expression level < 1%
End point description:	
OS is defined as the time between the date of randomization and the date of death. Median based on Kaplan-Meier Estimates.	
End point type	Secondary
End point timeframe:	
From randomization to date of death (up to approximately 45 months)	

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	350		
Units: Months				
median (confidence interval 95%)	99999 (41.72 to 99999)	99999 (99999 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio OS - all randomized with PD-L1 <1%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	697
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.73

Secondary: Recurrence-free Survival (RFS) by Baseline Tumor PD-L1 Expression

End point title	Recurrence-free Survival (RFS) by Baseline Tumor PD-L1 Expression

End point description:

RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma (including melanoma in situ), or death (from any cause), whichever occurred first. Median based on Kaplan-Meier Estimates. PD-L1 expression levels based on clinical database.

End point type	Secondary

End point timeframe:

From randomization to Study Completion Date (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	920	924		
Units: Months				
median (confidence interval 95%)				

< 1% Tumor PD-L1 Expression	33.18 (22.21 to 99999)	25.33 (19.81 to 99999)		
≥ 1% Tumor PD-L1 Expression	99999 (99999 to 99999)	99999 (99999 to 99999)		
≥ 5% Tumor PD-L1 Expression	99999 (99999 to 99999)	99999 (99999 to 99999)		
< 5% Tumor PD-L1 Expression	99999 (31.18 to 99999)	99999 (27.63 to 99999)		
Non-quantifiable Tumor PD-L1 Expression	99999 (22.41 to 99999)	99999 (10.87 to 99999)		

Statistical analyses

Statistical analysis title	HR - tumor PD-L1 < 1%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	1844
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.14

Statistical analysis title	HR - tumor PD-L1 >= 1%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	1844
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.18

Statistical analysis title	HR - tumor PD-L1 >= 5%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo

Number of subjects included in analysis	1844
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.34

Statistical analysis title	HR - tumor PD-L1 < 5%
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	1844
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.1

Statistical analysis title	HR - tumor PD-L1 not quantifiable
Comparison groups	Arm A: Nivo + Ipi v Arm B: Nivo
Number of subjects included in analysis	1844
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.51

Secondary: Time to Next-Line Therapies - all randomized participants

End point title	Time to Next-Line Therapies - all randomized participants

End point description:

Time to next therapy was defined as the time from the date of randomization to the start date of next systemic therapy. Participants who did not receive next treatment were censored at the last known alive date. Time to second next therapy was defined as the time from the date of randomization to the start date of second next systemic therapy. Participants who did not receive second next treatment were censored at the last known alive date.

End point type	Secondary

End point timeframe:

From randomization to start of next therapy or second next therapy (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	920	924		
Units: Months				
median (confidence interval 95%)				
Time to next therapy	99999 (99999 to 99999)	99999 (99999 to 99999)		
Time to second next therapy	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Next-Line Therapies - all randomized participants with PD-L1 expression level < 1%

End point title	Time to Next-Line Therapies - all randomized participants with PD-L1 expression level < 1%

End point description:

Time to next therapy was defined as the time from the date of randomization to the start date of next systemic therapy. Participants who did not receive next treatment were censored at the last known alive date. Time to second next therapy was defined as the time from the date of randomization to the start date of second next systemic therapy. Participants who did not receive second next treatment were censored at the last known alive date

End point type	Secondary

End point timeframe:

From randomization to start of next therapy or second next therapy (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	351		
Units: Months				
median (confidence interval 95%)				
Time to next therapy	99999 (99999 to 99999)	99999 (99999 to 99999)		
Time to second next therapy	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Next Therapy to Second Next Therapy - all randomized participants

End point title	Time From Next Therapy to Second Next Therapy - all randomized participants

End point description:

Time from next treatment to second next treatment was defined as the time from the start date of next systemic therapy to start date of second next systemic therapy. No censoring rules were applied here as analysis was only performed for the subset of participants who received second next treatment.

End point type	Secondary

End point timeframe:

From start of first next systemic therapy to start of second next systemic therapy (up to approximately 28 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: Months				
median (full range (min-max))	4.60 (0.8 to 23.7)	4.80 (0.0 to 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Next Therapy to Second Next Therapy - all randomized participants with PD-L1 expression level < 1%

End point title	Time From Next Therapy to Second Next Therapy - all randomized participants with PD-L1 expression level < 1%

End point description:

Time from next treatment to second next treatment was defined as the time from the start date of next systemic therapy to start date of second next systemic therapy. No censoring rules were applied here as analysis was only performed for the subset of participants who received second next treatment.

End point type	Secondary

End point timeframe:

From start of first next systemic therapy to start of second next systemic therapy (up to approximately 28 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	46		
Units: Months				
median (full range (min-max))	4.44 (0.8 to 23.7)	5.04 (0.9 to 27.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) on next-line therapy - all randomized participants

End point title	Progression-free survival (PFS) on next-line therapy - all randomized participants

End point description:

PFS2 was defined as the time from randomization to the progression date on next-line systemic therapy or the end date of next-line systemic therapy (if progression date not available) or death from any cause (if both progression date and end date not available), and to last known alive date in case of no event (ie, censoring), meaning either (1) no subsequent systemic therapy and no death OR (2) subsequent systemic therapy but no progression date nor end date available and no death.

End point type	Secondary

End point timeframe:

From randomization to progression event (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	920	924		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) on next-line therapy - all randomized participants with PD-L1 expression level < 1%

End point title	Progression-free survival (PFS) on next-line therapy - all randomized participants with PD-L1 expression level < 1%

End point description:

PFS2 was defined as the time from randomization to the progression date on next-line systemic therapy or the end date of next-line systemic therapy (if progression date not available) or death from any cause (if both progression date and end date not available), and to last known alive date in case of no event (ie, censoring), meaning either (1) no subsequent systemic therapy and no death OR (2) subsequent systemic therapy but no progression date nor end date available and no death.

End point type	Secondary

End point timeframe:

From randomization to progression event (up to approximately 45 months)

End point values	Arm A: Nivo + Ipi	Arm B: Nivo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	349	351		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (35.94 to 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose to 30 days after last dose	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups	
Reporting group title	Nivolumab Monotherapy
Reporting group description:	
Nivolumab Monotherapy: Subjects were infused 480 mg of Nivolumab for 30 minutes on Day 1 of each treatment cycle every 4 weeks for one year	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab + Ipilimumab: Subjects were infused 240 milligram (mg) of Nivolumab for 30 minutes on Day 1 every 2 weeks plus Ipilimumab 1 mg/kg for 30 minutes every 6 weeks for one year	

Serious adverse events	Nivolumab Monotherapy	Nivolumab + Ipilimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	185 / 917 (20.17%)	308 / 916 (33.62%)	
number of deaths (all causes)	121	122	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	22 / 917 (2.40%)	13 / 916 (1.42%)	
occurrences causally related to treatment / all	0 / 32	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 917 (0.11%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			

subjects affected / exposed	6 / 917 (0.65%)	6 / 916 (0.66%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 1	
Marginal zone lymphoma			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma recurrent			
subjects affected / exposed	1 / 917 (0.11%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to breast			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			
subjects affected / exposed	1 / 917 (0.11%)	4 / 916 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	2 / 917 (0.22%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			

subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm progression			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal squamous cell carcinoma			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloma			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 917 (0.22%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent cancer			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schwannoma			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	10 / 917 (1.09%)	8 / 916 (0.87%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granuloma			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lithiasis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 917 (0.11%)	9 / 916 (0.98%)	
occurrences causally related to treatment / all	0 / 1	4 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Autoimmune disorder			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	1 / 917 (0.11%)	6 / 916 (0.66%)	
occurrences causally related to treatment / all	0 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic spasm			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated pneumonitis			
subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	2 / 917 (0.22%)	8 / 916 (0.87%)	
occurrences causally related to treatment / all	2 / 2	8 / 8	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amylase increased			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin I increased			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft complication			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head injury			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	3 / 917 (0.33%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 917 (0.00%)	4 / 916 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory distress			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiomegaly			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Autoimmune neuropathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery dissection			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 917 (0.33%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningism			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miller Fisher syndrome			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neuropathy peripheral			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	3 / 917 (0.33%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Orbital myositis			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	2 / 917 (0.22%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	1 / 917 (0.11%)	8 / 916 (0.87%)	
occurrences causally related to treatment / all	1 / 1	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	4 / 917 (0.44%)	21 / 916 (2.29%)	
occurrences causally related to treatment / all	4 / 4	23 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 917 (0.55%)	17 / 916 (1.86%)	
occurrences causally related to treatment / all	4 / 5	17 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epigastric discomfort			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 917 (0.11%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated enterocolitis			
subjects affected / exposed	3 / 917 (0.33%)	15 / 916 (1.64%)	
occurrences causally related to treatment / all	2 / 3	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal fibrosis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 917 (0.00%)	11 / 916 (1.20%)	
occurrences causally related to treatment / all	0 / 0	12 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis sclerosing			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	2 / 917 (0.22%)	5 / 916 (0.55%)	
occurrences causally related to treatment / all	2 / 2	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune-mediated hepatitis			

subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular regenerative hyperplasia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 917 (0.22%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 917 (0.33%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune nephritis			
subjects affected / exposed	2 / 917 (0.22%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephritis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Addison's disease			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal insufficiency			
subjects affected / exposed	1 / 917 (0.11%)	8 / 916 (0.87%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism primary			

subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	0 / 917 (0.00%)	5 / 916 (0.55%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	6 / 917 (0.65%)	18 / 916 (1.97%)	
occurrences causally related to treatment / all	6 / 6	19 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 917 (0.00%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Primary adrenal insufficiency			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis acute			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyrotoxic crisis			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 917 (0.11%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis-like syndrome			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Adrenalitis			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis infective			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter colitis			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 917 (0.44%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	2 / 917 (0.22%)	4 / 916 (0.44%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	3 / 917 (0.33%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes oesophagitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected bite			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 917 (0.11%)	3 / 916 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis aseptic			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Picornavirus infection			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 917 (0.11%)	8 / 916 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 917 (0.22%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	1 / 917 (0.11%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fulminant type 1 diabetes mellitus			
subjects affected / exposed	1 / 917 (0.11%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 917 (0.33%)	4 / 916 (0.44%)	
occurrences causally related to treatment / all	3 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 917 (0.22%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	0 / 917 (0.00%)	2 / 916 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	2 / 917 (0.22%)	0 / 916 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 917 (0.00%)	1 / 916 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Nivolumab Monotherapy	Nivolumab + Ipilimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	882 / 917 (96.18%)	894 / 916 (97.60%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	46 / 917 (5.02%)	42 / 916 (4.59%)	
occurrences (all)	73	58	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	143 / 917 (15.59%)	159 / 916 (17.36%)	
occurrences (all)	271	284	
Fatigue			
subjects affected / exposed	334 / 917 (36.42%)	339 / 916 (37.01%)	
occurrences (all)	505	503	
Influenza like illness			
subjects affected / exposed	45 / 917 (4.91%)	56 / 916 (6.11%)	
occurrences (all)	60	72	
Pyrexia			
subjects affected / exposed	79 / 917 (8.62%)	112 / 916 (12.23%)	
occurrences (all)	94	142	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	166 / 917 (18.10%)	160 / 916 (17.47%)	
occurrences (all)	216	214	
Dyspnoea			
subjects affected / exposed	65 / 917 (7.09%)	66 / 916 (7.21%)	
occurrences (all)	72	85	
Oropharyngeal pain			
subjects affected / exposed	43 / 917 (4.69%)	50 / 916 (5.46%)	
occurrences (all)	48	55	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	46 / 917 (5.02%)	30 / 916 (3.28%)	
occurrences (all)	56	34	
Insomnia			
subjects affected / exposed	68 / 917 (7.42%)	78 / 916 (8.52%)	
occurrences (all)	79	91	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	81 / 917 (8.83%)	129 / 916 (14.08%)	
occurrences (all)	129	239	
Amylase increased			
subjects affected / exposed	33 / 917 (3.60%)	79 / 916 (8.62%)	
occurrences (all)	60	142	
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 917 (7.20%)	107 / 916 (11.68%)	
occurrences (all)	92	159	
Blood creatine phosphokinase increased			
subjects affected / exposed	50 / 917 (5.45%)	54 / 916 (5.90%)	
occurrences (all)	67	75	
Lipase increased			
subjects affected / exposed	52 / 917 (5.67%)	115 / 916 (12.55%)	
occurrences (all)	95	240	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	45 / 917 (4.91%)	56 / 916 (6.11%)	
occurrences (all)	80	87	
Nervous system disorders			
Dizziness			
subjects affected / exposed	60 / 917 (6.54%)	62 / 916 (6.77%)	
occurrences (all)	73	78	
Headache			
subjects affected / exposed	207 / 917 (22.57%)	266 / 916 (29.04%)	
occurrences (all)	336	420	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	77 / 917 (8.40%)	99 / 916 (10.81%)	
occurrences (all)	105	131	
Abdominal pain upper			
subjects affected / exposed	35 / 917 (3.82%)	54 / 916 (5.90%)	
occurrences (all)	42	67	
Constipation			
subjects affected / exposed	87 / 917 (9.49%)	98 / 916 (10.70%)	
occurrences (all)	112	124	
Diarrhoea			
subjects affected / exposed	301 / 917 (32.82%)	327 / 916 (35.70%)	
occurrences (all)	521	595	
Dry mouth			
subjects affected / exposed	87 / 917 (9.49%)	95 / 916 (10.37%)	
occurrences (all)	94	108	
Nausea			
subjects affected / exposed	180 / 917 (19.63%)	213 / 916 (23.25%)	
occurrences (all)	270	308	
Vomiting			
subjects affected / exposed	73 / 917 (7.96%)	95 / 916 (10.37%)	
occurrences (all)	99	119	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	236 / 917 (25.74%)	337 / 916 (36.79%)	
occurrences (all)	324	507	
Rash			
subjects affected / exposed	229 / 917 (24.97%)	254 / 916 (27.73%)	
occurrences (all)	342	374	
Vitiligo			
subjects affected / exposed	55 / 917 (6.00%)	46 / 916 (5.02%)	
occurrences (all)	63	49	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	6 / 917 (0.65%)	48 / 916 (5.24%)	
occurrences (all)	8	52	
Hyperthyroidism			

subjects affected / exposed	98 / 917 (10.69%)	179 / 916 (19.54%)	
occurrences (all)	115	211	
Hypophysitis			
subjects affected / exposed	10 / 917 (1.09%)	84 / 916 (9.17%)	
occurrences (all)	10	94	
Hypothyroidism			
subjects affected / exposed	134 / 917 (14.61%)	208 / 916 (22.71%)	
occurrences (all)	161	253	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	205 / 917 (22.36%)	158 / 916 (17.25%)	
occurrences (all)	356	253	
Back pain			
subjects affected / exposed	92 / 917 (10.03%)	89 / 916 (9.72%)	
occurrences (all)	115	108	
Myalgia			
subjects affected / exposed	80 / 917 (8.72%)	90 / 916 (9.83%)	
occurrences (all)	106	114	
Pain in extremity			
subjects affected / exposed	50 / 917 (5.45%)	44 / 916 (4.80%)	
occurrences (all)	70	55	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	100 / 917 (10.91%)	108 / 916 (11.79%)	
occurrences (all)	129	152	
Upper respiratory tract infection			
subjects affected / exposed	82 / 917 (8.94%)	67 / 916 (7.31%)	
occurrences (all)	114	82	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	60 / 917 (6.54%)	104 / 916 (11.35%)	
occurrences (all)	79	125	
Hyperglycaemia			
subjects affected / exposed	46 / 917 (5.02%)	45 / 916 (4.91%)	
occurrences (all)	68	66	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2017	Study design changes
11 March 2019	Statistical analysis design modifications

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported