Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab Versus Ipilimumab Monotherapy in Subjects With Previously Untreated Unresectable or Metastatic Melanoma

Summary

EudraCT number	2012-005371-13
Trial protocol	BE DE IT AT FI GB IE CZ NL ES NO DK PL SE
Global end of trial date	19 April 2024

Results information

Result version number	v1 (current)
This version publication date	19 April 2025
First version publication date	19 April 2025

Trial information

Trial identification

Sponsor protocol code	CA209-067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01844505
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium,
Public contact	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com
Scientific contact	Global Submission Management, Clinical Trials, Bristol-Myers Squibb International Corporation, mg-gsm-ct@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to show that Nivolumab and/or Nivolumab in combination with Ipilimumab will extend progression free survival and overall survival compared to Ipilimumab alone.

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 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 107
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Denmark: 24
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Ireland: 27
Country: Number of subjects enrolled	Israel: 16
Country: Number of subjects enrolled	Italy: 100
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	New Zealand: 8
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Sweden: 6

Country: Number of subjects enrolled	Switzerland: 23
Country: Number of subjects enrolled	United Kingdom: 93
Country: Number of subjects enrolled	United States: 207
Worldwide total number of subjects	945
EEA total number of subjects	444

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	565
From 65 to 84 years	365
85 years and over	15

Subject disposition

Recruitment

Recruitment details:

The "Completed" category in the Treatment Period stands for "Participant not continuing in the treatment period".

Pre-assignment

Screening details:

Participants were enrolled in 21 countries.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab

Arm description:

Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity

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

Dosage and administration details:

Administered once every 2 weeks (Q2W)

Arm title	Nivolumab + Ipilimumab

Arm description:

Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity

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

Dosage and administration details:

Administered once every 3 weeks

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

Dosage and administration details:

Administered once every 2 weeks (Q2W)

Arm title	Ipilimumab

Arm description:	
Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses	
Arm type	Active comparator
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Administered once every 3 weeks	

Number of subjects in period 1	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab
Started	316	314	315
Completed	313	313	311
Not completed	3	1	4
Not Treated	3	1	4

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
Arms	
Are arms mutually exclusive?	Yes
Arm title	Nivolumab
Arm description:	
Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity	
Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use
Dosage and administration details:	
Administered once every 2 weeks (Q2W)	
Arm title	Nivolumab + Ipilimumab
Arm description:	
Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity	
Arm type	Experimental

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

Dosage and administration details:

Administered once every 2 weeks (Q2W)

Arm title	Ipilimumab

Arm description:

Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses

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

Dosage and administration details:

Administered once every 3 weeks

Number of subjects in period 2	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab
Started	313	313	311
Completed	313	313	311

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab
Reporting group description:	
Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses	

Reporting group values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab
Number of subjects	316	314	315
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	198	185	182
From 65-84 years	111	125	129
85 years and over	7	4	4
Age Continuous Units: years			
arithmetic mean	58.7	59.3	60.8
standard deviation	± 13.92	± 13.86	± 13.23
Sex: Female, Male Units:			
Female	114	108	113
Male	202	206	202
Race/Ethnicity, Customized Units: Subjects			
WHITE	308	310	303
BLACK OR AFRICAN AMERICAN	0	0	0
ASIAN	2	2	6
AMERICAN INDIAN OR ALASKA NATIVE	1	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	0	0
OTHER	4	2	5
NOT REPORTED	0	0	1

Reporting group values	Total		
Number of subjects	945		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	565		
From 65-84 years	365		
85 years and over	15		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units:			
Female	335		
Male	610		
Race/Ethnicity, Customized Units: Subjects			
WHITE	921		
BLACK OR AFRICAN AMERICAN	0		
ASIAN	10		
AMERICAN INDIAN OR ALASKA NATIVE	1		
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1		
OTHER	11		
NOT REPORTED	1		

End points

End points reporting groups

Reporting group title	Nivolumab
Reporting group description:	
Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab
Reporting group description:	
Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses	
Reporting group title	Nivolumab
Reporting group description:	
Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity	
Reporting group title	Nivolumab + Ipilimumab
Reporting group description:	
Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity	
Reporting group title	Ipilimumab
Reporting group description:	
Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses	

Primary: Progression Free Survival (PFS) - Primary

End point title	Progression Free Survival (PFS) - Primary
End point description:	
PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the Investigator, or death due to any cause, whichever occurred first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or die were censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die were censored on their date of randomization. Participants treated beyond progression were considered to have progressive disease at the time of the initial progression event regardless of subsequent tumor response. Particpants who started anti-cancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.	
End point type	Primary
End point timeframe:	
From randomization until disease progression or death, whichever occurred first (assessed up to February 2015, approximately 20 months)	

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: months				
median (confidence interval 95%)	6.87 (4.34 to 9.46)	11.50 (8.90 to 16.72)	2.89 (2.79 to 3.42)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	Other: 99.5 %
sides	2-sided
lower limit	0.43
upper limit	0.76

Statistical analysis title	Analysis 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log Rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	Other: 99.5 %
sides	2-sided
lower limit	0.31
upper limit	0.57

Primary: Rate of Overall Survival

End point title	Rate of Overall Survival[1]

End point description:

OS was defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS was censored on the last date the participant was known to be

alive. The overall survival rate at time T (6, 12, or 24 months) was defined as the probability that a participant was alive at time T following randomization.

End point type	Primary

End point timeframe:

24 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: Not required as per statistical design for those arms.

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: Probability of survival at Time T				
number (confidence interval 95%)				
Rate of OS at 6 months	0.85 (0.81 to 0.89)	0.86 (0.81 to 0.89)	0.82 (0.78 to 0.86)	
Rate of OS at 12 months	0.74 (0.69 to 0.79)	0.73 (0.68 to 0.78)	0.67 (0.61 to 0.72)	
Rate of OS at 24 months	0.59 (0.53 to 0.64)	0.64 (0.59 to 0.69)	0.45 (0.39 to 0.50)	

Statistical analyses

No statistical analyses for this end point

Primary: Overall Survival (OS)-Primary

End point title	Overall Survival (OS)-Primary

End point description:

OS was defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS was censored on the last date the participant was known to be alive.

End point type	Primary

End point timeframe:

From randomization to date of death (Assessed up to September 2016, approximately 39 months)

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[2]	314[3]	315[4]	
Units: months				
median (confidence interval 95%)	99999 (29.08 to 99999)	99999 (99999 to 99999)	19.98 (17.08 to 24.61)	

Notes:

[2] - 99999 stands for Not Estimable

[3] - 99999 stands for Not Estimable

[4] - 99999 stands for Not Estimable

Statistical analyses

Statistical analysis title	Analysis 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.55
Confidence interval	
level	Other: 98 %
sides	2-sided
lower limit	0.42
upper limit	0.72

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	Other: 98 %
sides	2-sided
lower limit	0.5
upper limit	0.78

Primary: Rate of Progression-Free Survival

End point title	Rate of Progression-Free Survival[5]

End point description:

PFS was defined as the time between the date of randomization and the first date of documented progression, as determined by the Investigator, or death due to any cause, whichever occurred first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or die were censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die were censored on their date of randomization. Participants treated beyond progression were considered to have progressive disease at the time of the initial progression event regardless of subsequent tumor response. Participants who started anti-cancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

End point type	Primary

End point timeframe:

24 months

Notes:

[5] - 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: Not required as per statistical design for those arms.

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: Percentage of participants				
number (confidence interval 95%)				
Rate at 6 months	0.52 (0.46 to 0.58)	0.63 (0.57 to 0.68)	0.28 (0.23 to 0.33)	
Rate at 12 months	0.43 (0.37 to 0.49)	0.50 (0.44 to 0.55)	0.18 (0.14 to 0.22)	
Rate at 24 months	0.37 (0.31 to 0.43)	0.43 (0.37 to 0.48)	0.12 (0.09 to 0.17)	

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 between the date of randomization and the first date of documented progression, as determined by the Investigator, or death due to any cause, whichever occurred first. Participants who died without a reported progression were considered to have progressed on the date of their death. Participants who did not progress or die were censored on the date of their last evaluable tumor assessment. Participants who did not have any on study tumor assessments and did not die were censored on their date of randomization. Participants treated beyond progression were considered to have progressive disease at the time of the initial progression event regardless of subsequent tumor response. Participants who started anti-cancer therapy without a prior reported progression were censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death, whichever occurred first (assessed up to approximately 128 months)

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: months				
median (confidence interval 95%)	6.93 (5.13 to 10.18)	11.50 (8.90 to 20.04)	2.86 (2.79 to 3.09)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.96

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS was censored on the last date the participant was known to be alive.

End point type	Secondary

End point timeframe:

From randomization until death (assessed up to approximately 128 months)

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: months				
median (confidence interval 95%)	36.93 (28.25 to 58.71)	71.92 (38.18 to 114.37)	19.94 (16.85 to 24.61)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.05

Secondary: Progression-Free Survival based on PD-L1 Expression Level

End point title	Progression-Free Survival based on PD-L1 Expression Level

End point description:

PD-L1 expression was defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an IHC assay. Tumor biopsy specimens without measurable PD-L1 expression were classified as indeterminate if the staining was hampered for reasons attributed to the biology of the specimen and not because of improper specimen preparation or handling. Missing specimens, specimens that were not optimally collected (ie not evaluable), and all other specimens were classified as unknown. Participants must have been classified as PD-L1 >=5% or PD-L1 <5% per a verified IHC assay, or as indeterminate (ie not unknown), in order to be randomized.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death from any cause, whichever occurs first (Assessed up to September 2016, approximately 39 months)

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[6]	314[7]	315[8]	
Units: months				
median (confidence interval 95%)				
PD-L1 < 1% (n=117, 123, 113)	2.83 (2.76 to 5.39)	11.17 (6.93 to 26.68)	2.76 (2.66 to 2.86)	
PD-L1 >= 1% (n= 171, 155, 164)	16.20 (8.11 to 27.66)	16.72 (9.72 to 99999)	3.48 (2.83 to 4.17)	
PD-L1 < 5% (n= 208, 210, 202)	5.32 (2.96 to 6.87)	11.17 (8.31 to 22.18)	2.83 (2.76 to 3.02)	
PD-L1 >= 5% (n= 80, 68, 75)	22.34 (9.46 to 99999)	22.11 (9.72 to 99999)	3.94 (2.79 to 4.21)	
PD-L1 < 10% (n= 229, 232, 223)	5.62 (3.09 to 8.87)	11.10 (8.02 to 18.14)	2.83 (2.76 to 3.02)	
PD-L1 >= 10% (n= 59, 46, 54)	21.98 (9.07 to 99999)	99999 (13.96 to 99999)	4.11 (2.79 to 5.59)	
PD-L1 Indeterminate/ Not Evaluable (n= 28, 36, 38)	2.99 (2.66 to 6.93)	6.93 (2.79 to 20.04)	2.83 (2.60 to 6.41)	

Notes:

[6] - 99999 stands for Not Estimable

[7] - 99999 stands for Not Estimable

[8] - 99999 stands for Not Estimable

Statistical analyses

Statistical analysis title	Analysis 3
Comparison groups	Nivolumab v Nivolumab + Ipilimumab

Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.87

Statistical analysis title	Analysis 4
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.59

Statistical analysis title	Analysis 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.54

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Ipilimumab

Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.85

Statistical analysis title	Analysis 7
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.71

Statistical analysis title	Analysis 8
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.53

Statistical analysis title	Analysis 9
Comparison groups	Nivolumab v Nivolumab + Ipilimumab

Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.94

Statistical analysis title	Analysis 10
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	0.6

Statistical analysis title	Analysis 11
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	0.54

Statistical analysis title	Analysis 12
Comparison groups	Nivolumab v Nivolumab + Ipilimumab

Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.38

Statistical analysis title	Analysis 13
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.67

Statistical analysis title	Analysis 14
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.54

Statistical analysis title	Analysis 5
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab

Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.53

Statistical analysis title	Analysis 6
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.21

Statistical analysis title	Analysis 18
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.09

Statistical analysis title	Analysis 17
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab

Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.49

Statistical analysis title	Analysis 16
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	0.73

Statistical analysis title	Analysis 15
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.01

Statistical analysis title	Analysis 19
Comparison groups	Nivolumab v Ipilimumab

Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.52

Statistical analysis title	Analysis 20
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.89

Statistical analysis title	Analysis 21
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.09

Secondary: Objective Response Rate (ORR) per Investigator Assessment

End point title	Objective Response Rate (ORR) per Investigator Assessment

End point description:

The ORR was defined as the percentage of participants with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized participants for each arm. The BOR was defined as the best response designation, as determined by the Investigator, recorded between the date of randomization and the date of progression, as assessed by the Investigator per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and

tumor-directed surgery), whichever occurred first. For participants without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations contributed to the BOR assessment. CR= Disappearance of all evidence of disease, confirmed by PET scan; PR= Regression of measureable disease and no new sites; Stable Disease (SD)= Failure to attain CR/PR or PD; Progressive Disease (PD)= Any new lesion or increase by >=50% of previously involved sites from nadir.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death, whichever occurred first (assessed up to approximately 128 months)

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	314	315	
Units: Percentage of participants				
number (confidence interval 95%)	44.9 (39.4 to 50.6)	58.3 (52.6 to 63.8)	19.0 (14.9 to 23.8)	

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.49
upper limit	5.16

Statistical analysis title	Analysis 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	6.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.38
upper limit	9.22

Statistical analysis title	Analysis 6
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of Objective Response Rates
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.7
upper limit	20.7

Statistical analysis title	Analysis 4
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of Objective Response Rates
Point estimate	39
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.2
upper limit	45.9

Statistical analysis title	Analysis 5
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Odds ratio (OR)
Point estimate	1.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.26
upper limit	2.42

Statistical analysis title	Analysis 3
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference of Objective Response Rates
Point estimate	26
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.1
upper limit	32.8

Secondary: Overall Survival based on PD-L1 Expression Level	
End point title	Overall Survival based on PD-L1 Expression Level
End point description:	
OS was defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS was censored on the last date the participant was known to be alive.	
End point type	Secondary
End point timeframe:	
From randomization until date of death (Assessed up to September 2016, approximately 39 months)	

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[9]	314[10]	315[11]	
Units: months				
median (confidence interval 95%)				
PD-L1 < 1% (n=117, 123, 113)	23.46 (13.01 to 99999)	99999 (26.45 to 99999)	18.56 (13.67 to 23.20)	
PD-L1 >= 1% (n= 171, 155, 164)	85.09 (39.00 to 99999)	82.30 (39.06 to 99999)	21.49 (16.85 to 29.08)	
PD-L1 < 5% (n= 208, 210, 202)	35.94 (23.06 to 59.24)	65.94 (32.72 to 114.37)	18.40 (13.70 to 22.51)	
PD-L1 >= 5% (n= 80, 68, 75)	64.51 (33.64 to 99999)	104.97 (39.06 to 99999)	28.88 (18.10 to 44.16)	
PD-L1 < 10% (n= 229, 232, 223)	36.93 (23.46 to 80.85)	70.74 (34.83 to 107.89)	18.56 (14.98 to 23.03)	
PD-L1 >= 10% (n= 59, 46, 54)	43.63 (31.24 to 99999)	99999 (39.06 to 99999)	29.08 (17.45 to 46.55)	
PD-L1 Indeterminate/ Not Evaluable (n= 28, 36, 38)	23.89 (11.76 to 99999)	99999 (21.39 to 99999)	18.73 (8.41 to 30.00)	

Notes:
[9] - 99999 stands for Not Estimable
[10] - 99999 stands for Not Estimable
[11] - 99999 stands for Not Estimable

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.05

Statistical analysis title	Analysis 2
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.81

Statistical analysis title	Analysis 12
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.53

Statistical analysis title	Analysis 11
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.91

Statistical analysis title	Analysis 10
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.91

Statistical analysis title	Analysis 9
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.08

Statistical analysis title	Analysis 8

Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.66

Statistical analysis title	Analysis 7
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.78

Statistical analysis title	Analysis 6
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.31

Statistical analysis title	Analysis 5
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab

Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.67

Statistical analysis title	Analysis 3
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.04

Statistical analysis title	Analysis 4
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.68

Statistical analysis title	Analysis 18
Comparison groups	Nivolumab v Nivolumab + Ipilimumab

Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.32

Statistical analysis title	Analysis 17
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.32
upper limit	0.91

Statistical analysis title	Analysis 16
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.1

Statistical analysis title	Analysis 15
Comparison groups	Nivolumab v Nivolumab + Ipilimumab

Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.14

Statistical analysis title	Analysis 21
Comparison groups	Nivolumab v Nivolumab + Ipilimumab
Number of subjects included in analysis	630
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.39

Statistical analysis title	Analysis 13
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.75

Statistical analysis title	Analysis 20
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab

Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.91

Statistical analysis title	Analysis 19
Comparison groups	Nivolumab v Ipilimumab
Number of subjects included in analysis	631
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.34

Statistical analysis title	Analysis 14
Comparison groups	Nivolumab + Ipilimumab v Ipilimumab
Number of subjects included in analysis	629
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	0.68

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Global Health Status

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the

exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[12]	314[13]	315[14]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	-2.8 (± 15.74)	-4.3 (± 21.38)	-3.1 (± 17.24)	
Week 7 (n= 239, 183, 218)	-2.6 (± 16.89)	-5.0 (± 20.60)	-4.3 (± 18.07)	
Week 11 (n= 201, 112, 163)	-2.0 (± 18.10)	-2.4 (± 21.99)	-6.2 (± 18.73)	
Week 13 (n= 195, 106, 130)	-1.9 (± 16.44)	-3.8 (± 21.21)	-5.5 (± 20.27)	
Week 17 (n= 158, 84, 104)	-1.6 (± 19.73)	-6.0 (± 22.01)	-6.1 (± 16.80)	
Week 19 (n= 164, 96, 98)	-0.8 (± 18.30)	-0.8 (± 21.70)	-5.4 (± 19.52)	
Week 23 (n= 134, 86, 75)	-2.8 (± 19.44)	-2.6 (± 22.00)	-3.7 (± 16.28)	
Week 25 (n= 144, 97, 75)	1.3 (± 17.39)	-3.3 (± 17.70)	-4.2 (± 16.52)	
Week 31 (n= 123, 92, 51)	2.5 (± 17.40)	1.5 (± 21.47)	2.0 (± 15.51)	
Week 37 (n= 116, 88, 48)	3.2 (± 18.44)	-0.2 (± 21.18)	-1.9 (± 15.11)	
Week 43 (n= 103, 74, 44)	3.5 (± 18.28)	-0.5 (± 23.04)	-0.9 (± 15.59)	
Week 49 (n= 97, 70, 40)	2.7 (± 16.52)	0.6 (± 21.95)	-0.4 (± 15.78)	
Week 55 (n= 86, 66, 34)	1.8 (± 14.26)	-2.4 (± 22.01)	0.7 (± 13.03)	
Week 61 (n= 85, 61, 31)	1.6 (± 16.29)	-3.6 (± 20.78)	0.8 (± 11.25)	
Week 67 (n= 76, 61, 29)	2.1 (± 17.49)	-2.9 (± 21.35)	-6.6 (± 15.17)	
Week 73 (n= 67, 54, 19)	0.1 (± 19.11)	-4.5 (± 21.76)	-3.5 (± 16.97)	
Week 79 (n= 67, 54, 21)	-0.1 (± 14.40)	-4.8 (± 20.51)	-0.8 (± 14.65)	
Week 85 (n= 68, 51, 18)	2.8 (± 16.64)	-3.3 (± 22.37)	0.0 (± 10.69)	
Week 91 (n= 62, 53, 16)	0.9 (± 17.08)	-3.9 (± 20.78)	0.5 (± 12.72)	
Week 97 (n= 58, 49, 17)	0.9 (± 17.01)	-5.1 (± 23.06)	-2.9 (± 12.13)	
Week 103 (n= 53, 46, 17)	2.2 (± 17.61)	-9.8 (± 19.03)	0.0 (± 13.50)	
Week 109 (n= 44, 39, 14)	2.8 (± 16.56)	-3.8 (± 23.17)	-2.4 (± 14.03)	
Week 115 (n= 44, 36, 17)	0.6 (± 15.50)	-6.9 (± 22.76)	-0.5 (± 11.59)	
Week 121 (n= 44, 39, 16)	1.1 (± 19.90)	-1.5 (± 19.20)	-3.1 (± 15.18)	
Week 127 (n= 47, 36, 17)	0.9 (± 20.06)	-1.9 (± 22.37)	1.5 (± 12.92)	
Week 133 (n= 29, 31, 11)	3.2 (± 20.70)	-2.4 (± 25.11)	3.8 (± 13.10)	
Week 139 (n= 20, 19, 6)	0.0 (± 18.73)	-4.4 (± 17.43)	5.6 (± 15.52)	
Week 145 (n= 14, 14, 6)	0.6 (± 25.42)	-8.9 (± 8.93)	-4.2 (± 17.28)	
Week 151 (n= 7, 7, 1)	3.6 (± 9.45)	-13.1 (± 9.45)	8.3 (± 99999)	
Week 157 (n= 1, 3, 0)	0.0 (± 99999)	-16.7 (± 8.33)	99999 (± 99999)	

Notes:

[12] - 99999 stands for Not Estimable

[13] - 99999 stands for Not Estimable

[14] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Social Functioning

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Social Functioning

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[15]	314[16]	315[17]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	-1.2 (± 21.99)	-4.6 (± 21.76)	-1.6 (± 21.59)	
Week 7 (n= 239, 183, 218)	-0.1 (± 20.58)	-5.8 (± 21.81)	-0.2 (± 21.79)	
Week 11 (n= 201, 112, 163)	-0.6 (± 22.32)	-5.1 (± 22.02)	-3.4 (± 21.53)	
Week 13 (n= 195, 106, 130)	0.6 (± 22.73)	-3.6 (± 20.57)	-2.2 (± 24.41)	
Week 17 (n= 158, 84, 104)	-0.9 (± 22.28)	-4.4 (± 25.10)	-2.9 (± 18.06)	
Week 19 (n= 164, 96, 98)	1.4 (± 21.40)	-1.7 (± 23.13)	-1.3 (± 24.71)	
Week 23 (n= 134, 86, 75)	-0.1 (± 19.87)	-1.2 (± 23.40)	-4.2 (± 21.94)	
Week 25 (n= 144, 97, 75)	1.2 (± 19.77)	-3.4 (± 21.37)	-1.3 (± 25.23)	
Week 31 (n= 123, 92, 51)	3.5 (± 16.84)	0.2 (± 20.30)	3.6 (± 22.68)	
Week 37 (n= 116, 88, 48)	1.6 (± 18.12)	1.1 (± 22.71)	3.1 (± 18.40)	
Week 43 (n= 103, 74, 44)	-0.2 (± 20.68)	2.9 (± 21.43)	4.2 (± 22.77)	
Week 49 (n= 97, 70, 40)	2.4 (± 17.35)	3.1 (± 19.92)	6.3 (± 18.37)	
Week 55 (n= 86, 66, 34)	0.6 (± 19.21)	0.0 (± 21.68)	5.9 (± 17.83)	
Week 61 (n= 85, 61, 31)	2.7 (± 16.44)	-0.5 (± 22.76)	5.9 (± 17.51)	
Week 67 (n= 76, 61, 29)	1.8 (± 16.46)	-0.8 (± 24.80)	-2.3 (± 17.66)	
Week 73 (n= 67, 54, 19)	1.5 (± 17.58)	-2.5 (± 17.85)	-8.8 (± 18.73)	
Week 79 (n= 67, 54, 21)	1.2 (± 14.01)	-3.4 (± 24.31)	0.8 (± 3.64)	

Week 85 (n= 68, 51, 18)	1.0 (± 13.77)	-7.5 (± 21.68)	-1.9 (± 7.86)	
Week 91 (n= 62, 53, 16)	-0.8 (± 17.96)	-5.7 (± 24.23)	1.0 (± 4.17)	
Week 97 (n= 58, 49, 17)	-0.3 (± 16.95)	-2.7 (± 22.14)	0.0 (± 0.00)	
Week 103 (n= 53, 46, 17)	-0.6 (± 17.28)	-4.3 (± 22.62)	-1.0 (± 4.04)	
Week 109 (n= 44, 39, 14)	4.2 (± 15.72)	-2.6 (± 20.43)	-3.6 (± 9.65)	
Week 115 (n= 44, 36, 17)	3.8 (± 18.63)	-2.3 (± 25.56)	0.0 (± 5.89)	
Week 121 (n= 44, 39, 16)	3.4 (± 19.88)	-3.0 (± 25.33)	-1.0 (± 4.17)	
Week 127 (n= 47, 36, 17)	3.5 (± 18.37)	-2.3 (± 22.24)	2.0 (± 5.54)	
Week 133 (n= 29, 31, 11)	0.6 (± 15.74)	-2.2 (± 26.44)	3.0 (± 10.05)	
Week 139 (n= 20, 19, 6)	4.2 (± 10.64)	-4.4 (± 19.12)	2.8 (± 16.39)	
Week 145 (n= 14, 14, 6)	-8.3 (± 26.75)	-11.9 (± 16.57)	2.8 (± 16.39)	
Week 151 (n= 7, 7, 1)	7.1 (± 23.29)	-9.5 (± 16.27)	0 (± 99999)	
Week 157 (n= 1, 3, 0)	0.0 (± 99999)	-22.2 (± 19.25)	99999 (± 99999)	

Notes:

[15] - 99999 stands for Not Estimable

[16] - 99999 stands for Not Estimable

[17] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Cognitive Functioning

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Cognitive Functioning

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[18]	314[19]	315[20]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	0.1 (± 12.28)	-2.1 (± 16.49)	-0.2 (± 13.99)	
Week 7 (n= 239, 183, 218)	-1.7 (± 12.80)	-3.6 (± 16.26)	-1.5 (± 13.36)	
Week 11 (n= 201, 112, 163)	-1.7 (± 13.27)	-0.1 (± 16.67)	-4.7 (± 15.33)	
Week 13 (n= 195, 106, 130)	-0.9 (± 13.45)	-0.3 (± 14.36)	-2.3 (± 14.64)	
Week 17 (n= 158, 84, 104)	-0.9 (± 12.79)	-3.6 (± 19.37)	-2.4 (± 13.43)	

Week 19 (n= 164, 96, 98)	-1.9 (± 13.99)	-1.0 (± 17.07)	-2.2 (± 13.39)	
Week 23 (n= 134, 86, 75)	-0.6 (± 13.31)	-4.5 (± 21.61)	-5.6 (± 14.58)	
Week 25 (n= 144, 97, 75)	-1.2 (± 12.72)	-4.8 (± 20.26)	-2.4 (± 12.46)	
Week 31 (n= 123, 92, 51)	1.1 (± 12.40)	-1.6 (± 17.13)	-3.3 (± 12.48)	
Week 37 (n= 116, 88, 48)	1.6 (± 11.42)	-2.8 (± 17.91)	-5.6 (± 15.88)	
Week 43 (n= 103, 74, 44)	-1.6 (± 15.40)	-2.9 (± 13.89)	0.0 (± 11.37)	
Week 49 (n= 97, 70, 40)	-1.2 (± 12.32)	-1.2 (± 15.10)	0.4 (± 12.22)	
Week 55 (n= 86, 66, 34)	0.4 (± 13.52)	-2.8 (± 14.79)	-2.5 (± 12.40)	
Week 61 (n= 85, 61, 31)	0.0 (± 14.09)	-1.6 (± 15.12)	-3.2 (± 15.76)	
Week 67 (n= 76, 61, 29)	-1.3 (± 13.27)	-3.0 (± 17.35)	-7.5 (± 16.42)	
Week 73 (n= 67, 54, 19)	-2.2 (± 11.20)	-4.9 (± 19.86)	-6.1 (± 11.40)	
Week 79 (n= 67, 54, 21)	-0.2 (± 12.48)	-4.6 (± 20.58)	-4.8 (± 13.06)	
Week 85 (n= 68, 51, 18)	-1.5 (± 12.79)	-4.2 (± 17.90)	-2.8 (± 13.10)	
Week 91 (n= 62, 53, 16)	-0.5 (± 12.06)	-4.7 (± 19.44)	-1.0 (± 9.56)	
Week 97 (n= 58, 49, 17)	-3.2 (± 14.12)	-3.7 (± 13.72)	-2.0 (± 10.00)	
Week 103 (n= 53, 46, 17)	-2.5 (± 15.81)	-5.8 (± 23.63)	-5.9 (± 15.52)	
Week 109 (n= 44, 39, 14)	1.1 (± 10.42)	-3.8 (± 19.29)	-1.2 (± 7.91)	
Week 115 (n= 44, 36, 17)	0.4 (± 9.84)	-3.7 (± 15.49)	-2.0 (± 10.00)	
Week 121 (n= 44, 39, 16)	-1.1 (± 14.56)	-7.7 (± 15.22)	-1.0 (± 9.56)	
Week 127 (n= 47, 36, 17)	-2.8 (± 17.83)	-3.2 (± 13.10)	-1.0 (± 13.78)	
Week 133 (n= 29, 31, 11)	-4.6 (± 22.67)	-3.8 (± 13.41)	1.5 (± 8.99)	
Week 139 (n= 20, 19, 6)	-3.3 (± 6.84)	-6.1 (± 11.40)	5.6 (± 8.61)	
Week 145 (n= 14, 14, 6)	-11.9 (± 29.55)	-4.8 (± 12.10)	-5.6 (± 17.21)	
Week 151 (n= 7, 7, 1)	-2.4 (± 11.50)	-7.1 (± 13.11)	16.7 (± 99999)	
Week 157 (n= 1, 3, 0)	0.0 (± 99999)	-11.1 (± 9.62)	99999 (± 99999)	

Notes:

[18] - 99999 stands for Not Estimable

[19] - 99999 stands for Not Estimable

[20] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Emotional Functioning

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Emotional Functioning

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[21]	314[22]	315[23]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	4.6 (± 15.91)	2.5 (± 16.44)	3.7 (± 17.21)	
Week 7 (n= 239, 183, 218)	4.0 (± 16.82)	2.0 (± 18.10)	3.1 (± 17.39)	
Week 11 (n= 201, 112, 163)	5.3 (± 14.84)	3.7 (± 15.57)	2.0 (± 18.89)	
Week 13 (n= 195, 106, 130)	3.8 (± 15.99)	4.3 (± 17.53)	2.9 (± 18.03)	
Week 17 (n= 158, 84, 104)	5.6 (± 16.54)	4.2 (± 18.81)	4.9 (± 15.86)	
Week 19 (n= 164, 96, 98)	5.8 (± 16.26)	6.2 (± 19.01)	6.5 (± 18.27)	
Week 23 (n= 134, 86, 75)	6.1 (± 17.04)	4.5 (± 20.20)	3.7 (± 18.85)	
Week 25 (n= 144, 97, 75)	6.6 (± 16.31)	2.1 (± 19.69)	5.9 (± 17.15)	
Week 31 (n= 123, 92, 51)	8.3 (± 15.57)	4.7 (± 15.64)	9.2 (± 16.69)	
Week 37 (n= 116, 88, 48)	9.6 (± 15.60)	6.8 (± 17.98)	5.9 (± 16.75)	
Week 43 (n= 103, 74, 44)	6.7 (± 18.89)	7.5 (± 18.36)	6.1 (± 14.86)	
Week 49 (n= 97, 70, 40)	5.8 (± 18.61)	7.1 (± 19.67)	8.1 (± 15.50)	
Week 55 (n= 86, 66, 34)	8.1 (± 18.57)	8.3 (± 16.79)	12.3 (± 15.11)	
Week 61 (n= 85, 61, 31)	7.9 (± 18.54)	7.9 (± 22.69)	9.9 (± 14.82)	
Week 67 (n= 76, 61, 29)	7.8 (± 19.97)	7.1 (± 20.52)	3.7 (± 15.36)	
Week 73 (n= 67, 54, 19)	8.0 (± 18.66)	4.5 (± 18.29)	4.8 (± 10.51)	
Week 79 (n= 67, 54, 21)	7.6 (± 19.56)	2.9 (± 23.36)	6.7 (± 10.41)	
Week 85 (n= 68, 51, 18)	6.4 (± 16.55)	3.3 (± 21.09)	7.9 (± 12.61)	
Week 91 (n= 62, 53, 16)	9.1 (± 17.77)	4.7 (± 20.25)	3.6 (± 12.53)	
Week 97 (n= 58, 49, 17)	5.3 (± 17.78)	3.9 (± 21.05)	3.9 (± 14.47)	
Week 103 (n= 53, 46, 17)	6.6 (± 19.50)	1.4 (± 23.46)	4.4 (± 12.88)	
Week 109 (n= 44, 39, 14)	8.3 (± 17.33)	4.1 (± 22.61)	12.5 (± 11.20)	
Week 115 (n= 44, 36, 17)	8.1 (± 21.15)	6.0 (± 21.23)	10.3 (± 10.84)	
Week 121 (n= 44, 39, 16)	8.3 (± 20.01)	4.5 (± 21.36)	9.4 (± 7.98)	
Week 127 (n= 47, 36, 17)	10.6 (± 17.61)	7.2 (± 21.19)	8.3 (± 13.50)	
Week 133 (n= 29, 31, 11)	7.5 (± 19.46)	8.3 (± 19.48)	9.1 (± 7.87)	
Week 139 (n= 20, 19, 6)	9.6 (± 11.87)	9.2 (± 16.87)	11.1 (± 10.09)	
Week 145 (n= 14, 14, 6)	2.4 (± 18.32)	6.0 (± 15.82)	11.1 (± 10.09)	
Week 151 (n= 7, 7, 1)	17.9 (± 16.27)	-2.4 (± 22.93)	16.7 (± 99999)	
Week 157 (n= 1, 3, 0)	16.7 (± 99999)	-11.1 (± 17.35)	99999 (± 99999)	

Notes:

[21] - 99999 stands for Not Estimable

[22] - 99999 stands for Not Estimable

[23] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Role Functioning

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Role Functioning

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[24]	314[25]	315[26]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	-4.1 (± 23.71)	-6.8 (± 24.90)	-4.4 (± 21.18)	
Week 7 (n= 239, 183, 218)	-3.6 (± 24.21)	-11.6 (± 28.25)	-4.9 (± 22.44)	
Week 11 (n= 201, 112, 163)	-3.2 (± 24.46)	-9.7 (± 28.97)	-6.1 (± 24.56)	
Week 13 (n= 195, 106, 130)	-3.1 (± 24.15)	-8.3 (± 25.33)	-6.9 (± 25.65)	
Week 17 (n= 158, 84, 104)	-3.2 (± 26.14)	-11.1 (± 27.05)	-6.3 (± 20.27)	
Week 19 (n= 164, 96, 98)	-1.3 (± 24.56)	-4.3 (± 25.04)	-6.1 (± 24.80)	
Week 23 (n= 134, 86, 75)	-2.6 (± 25.76)	-6.4 (± 24.14)	-8.4 (± 24.56)	
Week 25 (n= 144, 97, 75)	0.7 (± 21.13)	-7.7 (± 23.70)	-7.8 (± 23.78)	
Week 31 (n= 123, 92, 51)	-0.7 (± 21.38)	-3.1 (± 24.82)	-3.9 (± 23.24)	
Week 37 (n= 116, 88, 48)	1.6 (± 22.94)	-3.2 (± 26.37)	-3.1 (± 21.92)	
Week 43 (n= 103, 74, 44)	1.0 (± 20.85)	-3.4 (± 26.46)	-1.1 (± 19.49)	
Week 49 (n= 97, 70, 40)	1.7 (± 20.62)	-1.2 (± 21.67)	-2.1 (± 21.08)	
Week 55 (n= 86, 66, 34)	1.6 (± 20.07)	-4.8 (± 21.03)	1.0 (± 16.89)	
Week 61 (n= 85, 61, 31)	0.4 (± 19.58)	-3.0 (± 24.82)	1.1 (± 21.05)	
Week 67 (n= 76, 61, 29)	0.7 (± 19.33)	-4.6 (± 25.84)	-1.7 (± 17.45)	
Week 73 (n= 67, 54, 19)	0.5 (± 19.24)	-5.6 (± 26.70)	-0.9 (± 17.10)	
Week 79 (n= 67, 54, 21)	-0.7 (± 18.45)	-8.3 (± 27.99)	-2.4 (± 12.12)	
Week 85 (n= 68, 51, 18)	-2.2 (± 16.26)	-9.8 (± 28.90)	0.9 (± 12.09)	
Week 91 (n= 62, 53, 16)	1.1 (± 22.76)	-10.7 (± 29.25)	2.1 (± 13.44)	
Week 97 (n= 58, 49, 17)	0.6 (± 23.77)	-7.5 (± 26.80)	0.0 (± 13.18)	
Week 103 (n= 53, 46, 17)	-0.6 (± 26.95)	-9.8 (± 23.46)	2.0 (± 10.00)	
Week 109 (n= 44, 39, 14)	1.1 (± 21.98)	-5.6 (± 22.73)	4.8 (± 10.19)	
Week 115 (n= 44, 36, 17)	1.1 (± 22.27)	-10.6 (± 28.77)	2.0 (± 11.61)	
Week 121 (n= 44, 39, 16)	0.4 (± 28.41)	-8.1 (± 26.73)	2.1 (± 14.75)	
Week 127 (n= 47, 36, 17)	1.4 (± 24.03)	-6.0 (± 26.17)	1.0 (± 7.15)	
Week 133 (n= 29, 31, 11)	1.1 (± 34.48)	-4.3 (± 24.33)	-1.5 (± 11.68)	
Week 139 (n= 20, 19, 6)	-5.8 (± 9.79)	-8.8 (± 18.73)	8.3 (± 13.94)	

Week 145 (n= 14, 14, 6)	-6.0 (± 34.96)	-10.7 (± 16.80)	0.0 (± 23.57)	
Week 151 (n= 7, 7, 1)	7.1 (± 26.97)	-14.3 (± 17.82)	0.0 (± 99999)	
Week 157 (n= 1, 3, 0)	0.0 (± 99999)	-11.1 (± 19.25)	99999 (± 99999)	

Notes:

[24] - 99999 stands for Not Estimable

[25] - 99999 stands for Not Estimable

[26] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Physical Functioning

End point title	Mean change from baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Physical Functioning

End point description:

Health Related Quality of Life was assessed using the EORTC QLQ-C30 questionnaire Version 3. With the exception of 2 items included in the global health/quality of life scale, for which responses range from 1 (Very poor) to 7 (Excellent), item responses range from 1 (Not at all) to 4 (Very much). Raw scores for the EORTC QLQ-C30 are transformed to a 0-100 metric such that higher scores for all functional scales and Global Health Status indicate better HRQoL; an increase from baseline indicates improvement in HRQoL compared to baseline.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Week 5, 7, 11, 13, 17, 19, 23, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, 103, 109, 115, 121, 127, 133, 139, 145, 151 and 157

End point values	Nivolumab	Nivolumab + Ipilimumab	Ipilimumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316[27]	314[28]	315[29]	
Units: Points on EORTC scale				
arithmetic mean (standard deviation)				
Week 5 (n= 233, 183, 221)	-2.6 (± 13.62)	-4.9 (± 14.52)	-5.2 (± 14.09)	
Week 7 (n= 239, 183, 218)	-2.4 (± 14.53)	-5.3 (± 14.92)	-5.1 (± 14.69)	
Week 11 (n= 201, 112, 163)	-2.4 (± 16.14)	-5.6 (± 13.76)	-6.3 (± 14.72)	
Week 13 (n= 195, 106, 130)	-1.7 (± 15.79)	-4.3 (± 14.11)	-5.0 (± 17.47)	
Week 17 (n= 158, 84, 104)	-1.4 (± 15.82)	-6.7 (± 17.27)	-3.7 (± 13.46)	
Week 19 (n= 164, 96, 98)	0.4 (± 14.14)	-3.7 (± 14.34)	-4.3 (± 17.70)	
Week 23 (n= 134, 86, 75)	0.9 (± 13.87)	-4.0 (± 15.59)	-5.5 (± 15.04)	
Week 25 (n= 144, 97, 75)	1.4 (± 11.02)	-4.2 (± 14.28)	-3.6 (± 16.19)	
Week 31 (n= 123, 92, 51)	1.9 (± 11.60)	-2.4 (± 12.91)	-2.9 (± 14.62)	
Week 37 (n= 116, 88, 48)	2.1 (± 13.57)	-0.8 (± 13.00)	-2.2 (± 13.71)	
Week 43 (n= 103, 74, 44)	1.9 (± 13.16)	-0.5 (± 13.55)	-1.7 (± 12.71)	
Week 49 (n= 97, 70, 40)	1.3 (± 12.08)	-0.1 (± 12.97)	0.2 (± 12.31)	
Week 55 (n= 86, 66, 34)	1.8 (± 11.68)	-2.9 (± 13.24)	0.2 (± 10.57)	
Week 61 (n= 85, 61, 31)	0.2 (± 11.65)	-2.1 (± 13.91)	-0.2 (± 11.35)	

Week 67 (n= 76, 61, 29)	0.9 (± 12.44)	-1.7 (± 13.22)	-3.9 (± 10.62)	
Week 73 (n= 67, 54, 19)	0.5 (± 14.38)	-3.5 (± 11.27)	-3.9 (± 7.80)	
Week 79 (n= 67, 54, 21)	-1.7 (± 7.99)	-4.3 (± 17.09)	-1.3 (± 6.54)	
Week 85 (n= 68, 51, 18)	-1.6 (± 12.86)	-3.5 (± 12.88)	-2.6 (± 6.11)	
Week 91 (n= 62, 53, 16)	-0.4 (± 13.27)	-4.2 (± 14.45)	0.0 (± 0.00)	
Week 97 (n= 58, 49, 17)	-0.4 (± 13.79)	-4.4 (± 16.53)	-0.8 (± 4.00)	
Week 103 (n= 53, 46, 17)	-1.5 (± 17.18)	-5.4 (± 15.63)	-2.4 (± 7.05)	
Week 109 (n= 44, 39, 14)	1.7 (± 14.74)	-1.2 (± 13.92)	-1.0 (± 3.56)	
Week 115 (n= 44, 36, 17)	0.2 (± 14.20)	-2.0 (± 15.10)	-0.8 (± 3.23)	
Week 121 (n= 44, 39, 16)	-0.3 (± 15.77)	-3.4 (± 13.58)	-2.5 (± 5.37)	
Week 127 (n= 47, 36, 17)	1.2 (± 17.21)	-3.0 (± 16.75)	-2.4 (± 5.75)	
Week 133 (n= 29, 31, 11)	0.2 (± 23.33)	0.4 (± 14.40)	-2.4 (± 6.16)	
Week 139 (n= 20, 19, 6)	0.4 (± 7.94)	-3.9 (± 11.40)	-3.3 (± 5.58)	
Week 145 (n= 14, 14, 6)	-1.4 (± 27.94)	-6.7 (± 9.06)	-6.7 (± 8.43)	
Week 151 (n= 7, 7, 1)	8.6 (± 17.52)	-9.5 (± 12.68)	0.0 (± 99999)	
Week 157 (n= 1, 3, 0)	0.0 (± 99999)	-17.8 (± 25.24)	99999 (± 99999)	

Notes:

[27] - 99999 stands for Not Estimable

[28] - 99999 stands for Not Estimable

[29] - 99999 stands for Not Estimable

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All cause mortality was collected from date of randomization till death due to any cause (up to approximately 128 months) and Serious and Other Adverse events were collected from first dose till 30 days after last dose (up to approximately 128 months).

Adverse event reporting additional description:

All cause mortality data was collected for all the randomized participants and serious and other adverse events were collected for all the treated participants.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	NIVOLUMAB

Reporting group description:

Nivolumab monotherapy 3 mg/kg intravenous (IV) once every 2 weeks (Q2W) until disease progression or unacceptable toxicity

Reporting group title	NIVOLUMAB+IPILIMUMAB

Reporting group description:

Nivolumab 1 mg/kg IV combined with Ipilimumab 3 mg/kg IV once every 3 weeks (Q3W) for 4 doses followed by nivolumab 3 mg/kg IV Q2W until disease progression or unacceptable toxicity

Reporting group title	IPILIMUMAB

Reporting group description:

Ipilimumab monotherapy 3 mg/kg IV Q3W for a total of 4 doses

Serious adverse events	NIVOLUMAB	NIVOLUMAB+IPILIMUMAB	IPILIMUMAB
Total subjects affected by serious adverse events			
subjects affected / exposed	187 / 313 (59.74%)	249 / 313 (79.55%)	205 / 311 (65.92%)
number of deaths (all causes)	191	172	241
number of deaths resulting from adverse events	55	51	61
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenoid cystic carcinoma of salivary gland			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	8 / 313 (2.56%)	3 / 313 (0.96%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 15	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Bowen's disease			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Desmoid tumour			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diffuse large B-cell lymphoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected metastasis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal metastasis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	4 / 313 (1.28%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm progression			
subjects affected / exposed	54 / 313 (17.25%)	38 / 313 (12.14%)	61 / 311 (19.61%)
occurrences causally related to treatment / all	0 / 60	0 / 43	0 / 66
deaths causally related to treatment / all	0 / 41	0 / 29	0 / 45
Metastasis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	9 / 313 (2.88%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 10	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papillary thyroid cancer			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic malignant melanoma			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	3 / 313 (0.96%)	1 / 313 (0.32%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to meninges			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 313 (0.32%)	4 / 313 (1.28%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	1 / 1	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypertension			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inferior vena caval occlusion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphorrhoea			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Hyperthermia			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	3 / 313 (0.96%)	10 / 313 (3.19%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 3	4 / 15	1 / 4
deaths causally related to treatment / all	0 / 2	0 / 5	0 / 1
Fatigue			
subjects affected / exposed	2 / 313 (0.64%)	6 / 313 (1.92%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	2 / 2	4 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chills			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site discharge			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Accidental death			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Inflammation			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	4 / 313 (1.28%)	30 / 313 (9.58%)	12 / 311 (3.86%)
occurrences causally related to treatment / all	1 / 6	14 / 32	6 / 15
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	3 / 313 (0.96%)	4 / 313 (1.28%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mucosal inflammation			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nodule			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 1
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Reproductive system and breast			

disorders			
Prostatitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejaculation failure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	3 / 313 (0.96%)	3 / 313 (0.96%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infiltration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung disorder			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngospasm			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic hydrothorax			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 313 (0.96%)	7 / 313 (2.24%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	2 / 3	2 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cough			

subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar disorder			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stridor			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 313 (0.64%)	3 / 313 (0.96%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 3	0 / 1
Pulmonary embolism			
subjects affected / exposed	3 / 313 (0.96%)	11 / 313 (3.51%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 3	0 / 11	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Pulmonary oedema			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	3 / 313 (0.96%)	8 / 313 (2.56%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	2 / 3	9 / 9	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychotic disorder			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delusion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 313 (0.32%)	4 / 313 (1.28%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	2 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device loosening			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device breakage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
General physical condition abnormal			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cortisol decreased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 313 (0.32%)	3 / 313 (0.96%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			

subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoradionecrosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pneumothorax			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention postoperative			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tibia fracture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac arrest			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Bradycardia			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 313 (0.64%)	4 / 313 (1.28%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute coronary syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericardial effusion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			

subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Guillain-Barre syndrome			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic coma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ataxia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intraventricular haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medullary compression syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy peripheral			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	3 / 313 (0.96%)	4 / 313 (1.28%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sensory disturbance			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 313 (1.60%)	4 / 313 (1.28%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 6	3 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bicytopenia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of chronic disease			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			

subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anal fistula			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			

subjects affected / exposed	6 / 313 (1.92%)	5 / 313 (1.60%)	7 / 311 (2.25%)
occurrences causally related to treatment / all	1 / 6	2 / 5	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Abdominal distension			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune pancreatitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 313 (1.28%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Colitis			
subjects affected / exposed	6 / 313 (1.92%)	33 / 313 (10.54%)	29 / 311 (9.32%)
occurrences causally related to treatment / all	3 / 7	38 / 38	34 / 36
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Constipation			
subjects affected / exposed	3 / 313 (0.96%)	5 / 313 (1.60%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	8 / 313 (2.56%)	40 / 313 (12.78%)	26 / 311 (8.36%)
occurrences causally related to treatment / all	2 / 9	39 / 46	28 / 32
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphangiectasia intestinal			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 0	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intussusception			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mesenteric vein thrombosis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	2 / 313 (0.64%)	9 / 313 (2.88%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 2	7 / 10	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated enterocolitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 313 (0.96%)	2 / 313 (0.64%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Retroperitoneal haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal prolapse			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 313 (0.64%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 313 (0.96%)	11 / 313 (3.51%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 4	7 / 14	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			

subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatorenal failure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatomegaly			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	2 / 313 (0.64%)	5 / 313 (1.60%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cytolysis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune hepatitis			
subjects affected / exposed	3 / 313 (0.96%)	6 / 313 (1.92%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	2 / 3	6 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal hypertension			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 313 (0.32%)	7 / 313 (2.24%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 313 (0.00%)	5 / 313 (1.60%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis bullous			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative generalised			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatomyositis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitic ulcer			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic epidermal necrolysis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin toxicity			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin oedema			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin lesion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin burning sensation			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash pruritic			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pemphigoid			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	1 / 2	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 313 (0.64%)	10 / 313 (3.19%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 2	4 / 10	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysuria			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerulonephritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated nephritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower urinary tract symptoms			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 313 (0.64%)	3 / 313 (0.96%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	2 / 3	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal insufficiency			
subjects affected / exposed	3 / 313 (0.96%)	7 / 313 (2.24%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	3 / 3	7 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenal haemorrhage			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorder			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glucocorticoid deficiency			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Secondary adrenocortical insufficiency			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypothyroidism			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypopituitarism			

subjects affected / exposed	1 / 313 (0.32%)	3 / 313 (0.96%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	1 / 313 (0.32%)	8 / 313 (2.56%)	8 / 311 (2.57%)
occurrences causally related to treatment / all	1 / 1	7 / 8	9 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	0 / 313 (0.00%)	6 / 313 (1.92%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperparathyroidism			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Goitre			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibromyalgia			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondrocalcinosis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyositis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain in extremity			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myopathy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal stiffness			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Biliary sepsis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess intestinal			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium bacteraemia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Citrobacter sepsis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	3 / 313 (0.96%)	3 / 313 (0.96%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bursitis infective			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	2 / 313 (0.64%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal perforated			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 313 (0.64%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			

subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 313 (0.32%)	3 / 313 (0.96%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Folliculitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia streptococcal			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	5 / 313 (1.60%)	3 / 313 (0.96%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peritonitis bacterial			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral candidiasis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 313 (0.96%)	9 / 313 (2.88%)	5 / 311 (1.61%)
occurrences causally related to treatment / all	0 / 3	1 / 9	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Staphylococcal infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 313 (0.64%)	3 / 313 (0.96%)	4 / 311 (1.29%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 313 (0.00%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 1
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hyperglycaemia			
subjects affected / exposed	1 / 313 (0.32%)	7 / 313 (2.24%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	1 / 1	3 / 12	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	1 / 313 (0.32%)	1 / 313 (0.32%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 313 (0.00%)	10 / 313 (3.19%)	3 / 311 (0.96%)
occurrences causally related to treatment / all	0 / 0	7 / 12	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 313 (0.00%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 313 (0.32%)	2 / 313 (0.64%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 313 (0.00%)	3 / 313 (0.96%)	2 / 311 (0.64%)
occurrences causally related to treatment / all	0 / 0	3 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolic acidosis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 313 (0.00%)	1 / 311 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Steroid diabetes			
subjects affected / exposed	1 / 313 (0.32%)	0 / 313 (0.00%)	0 / 311 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	NIVOLUMAB	NIVOLUMAB+IPILIMUMAB	IPILIMUMAB
Total subjects affected by non-serious adverse events			
subjects affected / exposed	302 / 313 (96.49%)	302 / 313 (96.49%)	302 / 311 (97.11%)
Vascular disorders			
Hypertension			
subjects affected / exposed	34 / 313 (10.86%)	26 / 313 (8.31%)	27 / 311 (8.68%)
occurrences (all)	56	54	34
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	64 / 313 (20.45%)	123 / 313 (39.30%)	61 / 311 (19.61%)
occurrences (all)	85	191	92
Pain			
subjects affected / exposed	18 / 313 (5.75%)	23 / 313 (7.35%)	29 / 311 (9.32%)
occurrences (all)	20	37	30
Oedema peripheral			
subjects affected / exposed	39 / 313 (12.46%)	39 / 313 (12.46%)	45 / 311 (14.47%)
occurrences (all)	44	46	51
Influenza like illness			
subjects affected / exposed	31 / 313 (9.90%)	28 / 313 (8.95%)	25 / 311 (8.04%)
occurrences (all)	38	41	30
Fatigue			
subjects affected / exposed	159 / 313 (50.80%)	168 / 313 (53.67%)	140 / 311 (45.02%)
occurrences (all)	210	249	185
Chills			
subjects affected / exposed	23 / 313 (7.35%)	35 / 313 (11.18%)	20 / 311 (6.43%)
occurrences (all)	26	40	23
Chest pain			
subjects affected / exposed	19 / 313 (6.07%)	12 / 313 (3.83%)	13 / 311 (4.18%)
occurrences (all)	20	17	14
Asthenia			
subjects affected / exposed	47 / 313 (15.02%)	50 / 313 (15.97%)	29 / 311 (9.32%)
occurrences (all)	83	61	36
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	20 / 313 (6.39%)	23 / 313 (7.35%)	17 / 311 (5.47%)
occurrences (all)	24	30	18

Nasal congestion			
subjects affected / exposed	21 / 313 (6.71%)	15 / 313 (4.79%)	8 / 311 (2.57%)
occurrences (all)	25	17	12
Dyspnoea exertional			
subjects affected / exposed	20 / 313 (6.39%)	8 / 313 (2.56%)	14 / 311 (4.50%)
occurrences (all)	23	10	16
Dyspnoea			
subjects affected / exposed	47 / 313 (15.02%)	72 / 313 (23.00%)	43 / 311 (13.83%)
occurrences (all)	54	90	51
Cough			
subjects affected / exposed	100 / 313 (31.95%)	82 / 313 (26.20%)	69 / 311 (22.19%)
occurrences (all)	155	115	96
Pneumonitis			
subjects affected / exposed	6 / 313 (1.92%)	17 / 313 (5.43%)	7 / 311 (2.25%)
occurrences (all)	8	21	8
Psychiatric disorders			
Insomnia			
subjects affected / exposed	44 / 313 (14.06%)	51 / 313 (16.29%)	42 / 311 (13.50%)
occurrences (all)	52	60	43
Depression			
subjects affected / exposed	12 / 313 (3.83%)	21 / 313 (6.71%)	9 / 311 (2.89%)
occurrences (all)	15	24	10
Anxiety			
subjects affected / exposed	11 / 313 (3.51%)	24 / 313 (7.67%)	19 / 311 (6.11%)
occurrences (all)	15	26	21
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 313 (7.99%)	69 / 313 (22.04%)	18 / 311 (5.79%)
occurrences (all)	33	89	21
Amylase increased			
subjects affected / exposed	23 / 313 (7.35%)	33 / 313 (10.54%)	17 / 311 (5.47%)
occurrences (all)	59	38	37
Aspartate aminotransferase increased			
subjects affected / exposed	25 / 313 (7.99%)	61 / 313 (19.49%)	19 / 311 (6.11%)
occurrences (all)	30	80	20
Blood alkaline phosphatase increased			

subjects affected / exposed	14 / 313 (4.47%)	19 / 313 (6.07%)	8 / 311 (2.57%)
occurrences (all)	15	22	9
Blood creatinine increased			
subjects affected / exposed	7 / 313 (2.24%)	25 / 313 (7.99%)	15 / 311 (4.82%)
occurrences (all)	8	31	22
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 313 (2.24%)	16 / 313 (5.11%)	10 / 311 (3.22%)
occurrences (all)	7	21	10
Lipase increased			
subjects affected / exposed	35 / 313 (11.18%)	51 / 313 (16.29%)	21 / 311 (6.75%)
occurrences (all)	88	67	61
Weight decreased			
subjects affected / exposed	28 / 313 (8.95%)	42 / 313 (13.42%)	26 / 311 (8.36%)
occurrences (all)	29	46	27
Cardiac disorders			
Tachycardia			
subjects affected / exposed	6 / 313 (1.92%)	16 / 313 (5.11%)	13 / 311 (4.18%)
occurrences (all)	6	18	13
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	23 / 313 (7.35%)	18 / 313 (5.75%)	17 / 311 (5.47%)
occurrences (all)	24	18	18
Headache			
subjects affected / exposed	79 / 313 (25.24%)	82 / 313 (26.20%)	78 / 311 (25.08%)
occurrences (all)	98	157	103
Dizziness			
subjects affected / exposed	33 / 313 (10.54%)	43 / 313 (13.74%)	30 / 311 (9.65%)
occurrences (all)	45	53	37
Dysgeusia			
subjects affected / exposed	17 / 313 (5.43%)	18 / 313 (5.75%)	8 / 311 (2.57%)
occurrences (all)	20	19	9
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 313 (11.18%)	41 / 313 (13.10%)	43 / 311 (13.83%)
occurrences (all)	39	56	52
Eye disorders			

Vision blurred			
subjects affected / exposed	18 / 313 (5.75%)	18 / 313 (5.75%)	15 / 311 (4.82%)
occurrences (all)	20	21	18
Dry eye			
subjects affected / exposed	17 / 313 (5.43%)	12 / 313 (3.83%)	8 / 311 (2.57%)
occurrences (all)	19	13	8
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	17 / 313 (5.43%)	9 / 313 (2.88%)	13 / 311 (4.18%)
occurrences (all)	21	12	16
Abdominal pain			
subjects affected / exposed	62 / 313 (19.81%)	59 / 313 (18.85%)	68 / 311 (21.86%)
occurrences (all)	77	82	89
Abdominal pain upper			
subjects affected / exposed	24 / 313 (7.67%)	24 / 313 (7.67%)	25 / 311 (8.04%)
occurrences (all)	24	27	31
Colitis			
subjects affected / exposed	9 / 313 (2.88%)	21 / 313 (6.71%)	15 / 311 (4.82%)
occurrences (all)	9	22	17
Constipation			
subjects affected / exposed	69 / 313 (22.04%)	63 / 313 (20.13%)	77 / 311 (24.76%)
occurrences (all)	91	97	98
Diarrhoea			
subjects affected / exposed	122 / 313 (38.98%)	168 / 313 (53.67%)	147 / 311 (47.27%)
occurrences (all)	247	405	277
Dyspepsia			
subjects affected / exposed	17 / 313 (5.43%)	12 / 313 (3.83%)	14 / 311 (4.50%)
occurrences (all)	26	17	14
Dry mouth			
subjects affected / exposed	28 / 313 (8.95%)	34 / 313 (10.86%)	17 / 311 (5.47%)
occurrences (all)	31	41	17
Vomiting			
subjects affected / exposed	69 / 313 (22.04%)	99 / 313 (31.63%)	60 / 311 (19.29%)
occurrences (all)	92	161	79
Nausea			

subjects affected / exposed	105 / 313 (33.55%)	136 / 313 (43.45%)	104 / 311 (33.44%)
occurrences (all)	170	232	158
Gastrooesophageal reflux disease			
subjects affected / exposed	19 / 313 (6.07%)	13 / 313 (4.15%)	14 / 311 (4.50%)
occurrences (all)	20	19	15
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	25 / 313 (7.99%)	16 / 313 (5.11%)	14 / 311 (4.50%)
occurrences (all)	32	18	14
Dry skin			
subjects affected / exposed	28 / 313 (8.95%)	30 / 313 (9.58%)	19 / 311 (6.11%)
occurrences (all)	29	35	21
Actinic keratosis			
subjects affected / exposed	17 / 313 (5.43%)	2 / 313 (0.64%)	1 / 311 (0.32%)
occurrences (all)	21	2	1
Vitiligo			
subjects affected / exposed	38 / 313 (12.14%)	29 / 313 (9.27%)	17 / 311 (5.47%)
occurrences (all)	43	31	17
Rash maculo-papular			
subjects affected / exposed	22 / 313 (7.03%)	44 / 313 (14.06%)	43 / 311 (13.83%)
occurrences (all)	26	55	57
Rash			
subjects affected / exposed	101 / 313 (32.27%)	111 / 313 (35.46%)	84 / 311 (27.01%)
occurrences (all)	145	159	104
Pruritus			
subjects affected / exposed	92 / 313 (29.39%)	126 / 313 (40.26%)	135 / 311 (43.41%)
occurrences (all)	151	200	167
Hyperhidrosis			
subjects affected / exposed	12 / 313 (3.83%)	22 / 313 (7.03%)	11 / 311 (3.54%)
occurrences (all)	13	29	11
Skin lesion			
subjects affected / exposed	20 / 313 (6.39%)	11 / 313 (3.51%)	9 / 311 (2.89%)
occurrences (all)	24	12	10
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	4 / 313 (1.28%)	16 / 313 (5.11%)	7 / 311 (2.25%)
occurrences (all)	4	17	7
Hyperthyroidism			
subjects affected / exposed	18 / 313 (5.75%)	30 / 313 (9.58%)	3 / 311 (0.96%)
occurrences (all)	20	34	11
Hypophysitis			
subjects affected / exposed	5 / 313 (1.60%)	20 / 313 (6.39%)	9 / 311 (2.89%)
occurrences (all)	5	20	11
Hypothyroidism			
subjects affected / exposed	38 / 313 (12.14%)	68 / 313 (21.73%)	17 / 311 (5.47%)
occurrences (all)	41	70	18
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	87 / 313 (27.80%)	79 / 313 (25.24%)	78 / 311 (25.08%)
occurrences (all)	121	125	87
Back pain			
subjects affected / exposed	58 / 313 (18.53%)	46 / 313 (14.70%)	53 / 311 (17.04%)
occurrences (all)	74	56	61
Groin pain			
subjects affected / exposed	17 / 313 (5.43%)	5 / 313 (1.60%)	8 / 311 (2.57%)
occurrences (all)	19	5	8
Muscle spasms			
subjects affected / exposed	22 / 313 (7.03%)	16 / 313 (5.11%)	16 / 311 (5.14%)
occurrences (all)	24	19	17
Muscular weakness			
subjects affected / exposed	13 / 313 (4.15%)	22 / 313 (7.03%)	12 / 311 (3.86%)
occurrences (all)	16	25	13
Musculoskeletal chest pain			
subjects affected / exposed	16 / 313 (5.11%)	13 / 313 (4.15%)	16 / 311 (5.14%)
occurrences (all)	19	13	24
Myalgia			
subjects affected / exposed	34 / 313 (10.86%)	33 / 313 (10.54%)	23 / 311 (7.40%)
occurrences (all)	36	43	26
Neck pain			

subjects affected / exposed	15 / 313 (4.79%)	18 / 313 (5.75%)	12 / 311 (3.86%)
occurrences (all)	21	18	13
Pain in extremity			
subjects affected / exposed	49 / 313 (15.65%)	38 / 313 (12.14%)	43 / 311 (13.83%)
occurrences (all)	57	40	48
Infections and infestations			
Sinusitis			
subjects affected / exposed	16 / 313 (5.11%)	14 / 313 (4.47%)	5 / 311 (1.61%)
occurrences (all)	20	25	6
Rhinitis			
subjects affected / exposed	20 / 313 (6.39%)	26 / 313 (8.31%)	10 / 311 (3.22%)
occurrences (all)	24	30	10
Nasopharyngitis			
subjects affected / exposed	43 / 313 (13.74%)	34 / 313 (10.86%)	29 / 311 (9.32%)
occurrences (all)	66	57	39
Influenza			
subjects affected / exposed	16 / 313 (5.11%)	20 / 313 (6.39%)	8 / 311 (2.57%)
occurrences (all)	19	24	8
Conjunctivitis			
subjects affected / exposed	5 / 313 (1.60%)	19 / 313 (6.07%)	6 / 311 (1.93%)
occurrences (all)	7	21	6
Upper respiratory tract infection			
subjects affected / exposed	32 / 313 (10.22%)	28 / 313 (8.95%)	17 / 311 (5.47%)
occurrences (all)	47	68	29
Urinary tract infection			
subjects affected / exposed	16 / 313 (5.11%)	23 / 313 (7.35%)	9 / 311 (2.89%)
occurrences (all)	31	35	10
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	76 / 313 (24.28%)	97 / 313 (30.99%)	76 / 311 (24.44%)
occurrences (all)	94	140	89
Dehydration			
subjects affected / exposed	7 / 313 (2.24%)	24 / 313 (7.67%)	17 / 311 (5.47%)
occurrences (all)	8	31	22
Hyperglycaemia			

subjects affected / exposed	9 / 313 (2.88%)	18 / 313 (5.75%)	17 / 311 (5.47%)
occurrences (all)	10	20	25
Hypoalbuminaemia			
subjects affected / exposed	6 / 313 (1.92%)	16 / 313 (5.11%)	9 / 311 (2.89%)
occurrences (all)	7	19	9
Hypokalaemia			
subjects affected / exposed	12 / 313 (3.83%)	37 / 313 (11.82%)	15 / 311 (4.82%)
occurrences (all)	16	42	21
Hyponatraemia			
subjects affected / exposed	7 / 313 (2.24%)	25 / 313 (7.99%)	14 / 311 (4.50%)
occurrences (all)	8	32	19

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2013	The main purpose of the first global amendment is to add a recommendation to perform an optional tumor biopsy when assessing whether to treat beyond progression per a Health Authority request. This biopsy can be used to assess the impact of treatment on relevant melanoma biomarkers including BRAF mutation status and investigate potential mechanisms of resistance to immunotherapeutic agents.
27 June 2014	The main purpose of Amendment 06 is to change the secondary objective to add PFS as a co-primary objective. Additional modification are as described below: Revise Research Hypothesis, Study Rationale, Primary Endpoints to include PFS as a co-primary objective/endpoint. Add rationale for inclusion of PFS as a co-primary endpoint. Revise statistical section 8 to include analyses related to PFS.
16 January 2015	The main purpose of Amendment 07 is to add the collection of radiographic images for review by an independent radiological review committee. No other changes are included in this amendment.
19 May 2015	The purpose of this amendment is to allow for future collection of survival status outside of the protocol-defined windows if necessary, correct errors and update Appendix 5 Methodsof Contraception as well as SAE reporting language.
12 October 2016	The main purpose of this protocol amendment is necessary following a recent update to the Nivolumab Investigator's Brochure version 15, Erratum 01, includingthose related to the use of contraceptives, and updatedAppendix 5. Additionally, updated Tumor Assessment scan frequencyin the Follow-up and Survival phase.
20 October 2017	Prior to implementation of this amendment, following completion of the primary efficacy analysis, maintenance of the blind was no longer required for study purposes and all subjects were unblinded.The purpose of this amendment is to provide instructions for unblinded subjects remaining on study treatment or in follow-up.
17 May 2021	The purpose of Protocol Amendment 08 is to extend the studyfor about an additional 2.5 years, to yield a total study duration of approximately 10 years.As a consequence, data associated with the primary, secondary, and exploratory efficacy outcomes will continue to be collected on case report forms. In addition, protocol clarifications and/or updates are provided.EQ-5D questionnaires after study drug discontinuation will be collected for up to 7.5 years since randomization.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported