



Clinical trial results:

Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Summary

EudraCT number	2015-004920-67
Trial protocol	DE ES DK GB NL PL IT
Global end of trial date	28 May 2021

Results information

Result version number	v1 (current)
This version publication date	06 June 2022
First version publication date	06 June 2022

Trial information

Trial identification

Sponsor protocol code	CA209-511
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Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	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	23 June 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naïve subjects with unresectable or metastatic melanoma.

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	04 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Canada: 33
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 110
Country: Number of subjects enrolled	Germany: 29
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 27
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	United States: 22
Worldwide total number of subjects	385
EEA total number of subjects	284

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)	252
From 65 to 84 years	131
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

387 participants were randomized, 385 were treated. Cohort C/N6I1 assessed for exploratory outcome measures not being reported in the Outcome Measures module. Safety data included with AE data.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV

Arm description:

nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks.

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:

1 mg/kg as a 30 minute IV infusion

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:

3 mg/kg was administered as a 30 minute IV infusion then flat dose 480 mg nivolumab IV as a 30-minute IV infusion

Arm title	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
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Arm description:

nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks

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:

1 mg/kg was administered as a 30 minute IV infusion then flat dose 480 mg nivolumab IV as a 30-minute IV infusion

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: 3 mg/kg as a 30 minute IV infusion	
Arm title	Cohort C, Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg

Arm description:

nivolumab 6 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 480 mg Flat Dose 4 weeks later and repeated every 8 weeks

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:

1 mg/kg as a 30 minute IV infusion

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:

6 mg/kg was administered as a 30 minute IV infusion then flat dose 480 mg nivolumab IV as a 30-minute IV infusion

Number of subjects in period 1	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV	Cohort C, Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Started	180	178	27
Completed	6	2	2
Not completed	174	176	25
Participant withdrew consent	2	2	-
Study drug toxicity	46	70	6
Not reported	9	6	-
Maximum clinical benefit	4	2	-
Request to discontinue treatment	1	4	1
Adverse event unrelated to study drug	13	6	1
Other reasons	6	6	-
Disease Progression	55	52	14
Completed treatment as per protocol	36	27	3
Administrative reason by sponsor	2	1	-

Baseline characteristics

Reporting groups

Reporting group title	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV
Reporting group description: nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks.	
Reporting group title	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Reporting group description: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks	
Reporting group title	Cohort C, Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Reporting group description: nivolumab 6 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 480 mg Flat Dose 4 weeks later and repeated every 8 weeks	

Reporting group values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV	Cohort C, Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Number of subjects	180	178	27
Age categorical Units: Subjects			
Adults (18-64 years)	115	120	17
From 65-84 years	64	57	10
85 years and over	1	1	0
Age Continuous Units: Years			
arithmetic mean	57.0	57.2	55.1
standard deviation	± 14.1	± 13.4	± 15.8
Sex: Female, Male Units:			
Female	75	77	11
Male	105	101	16
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	2	1
White	174	168	23
More than one race	0	0	0
Unknown or Not Reported	5	8	2

Reporting group values	Total		
Number of subjects	385		
Age categorical Units: Subjects			
Adults (18-64 years)	252		
From 65-84 years	131		
85 years and over	2		

Age Continuous Units: Years arithmetic mean standard deviation	-		
Sex: Female, Male Units:			
Female	163		
Male	222		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	2		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	3		
White	365		
More than one race	0		
Unknown or Not Reported	15		

End points

End points reporting groups

Reporting group title	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV
Reporting group description: nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks.	
Reporting group title	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Reporting group description: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks	
Reporting group title	Cohort C, Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Reporting group description: nivolumab 6 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 480 mg Flat Dose 4 weeks later and repeated every 8 weeks	

Primary: The Percentage of Participants with Drug-Related Grade 3 - 5 Adverse Events (AEs)

End point title	The Percentage of Participants with Drug-Related Grade 3 - 5 Adverse Events (AEs) ^[1]
End point description: The percentage of participants who experienced at least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment. AE grade was defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.	
End point type	Primary
End point timeframe: From first dose of study treatment up to primary completion date 20-Apr-2017 (up to approximately 12 months)	
Notes: [1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module	

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: Percentage of participants				
number (confidence interval 95%)	32.8 (26.0 to 40.2)	45.5 (38.0 to 53.1)		

Statistical analyses

Statistical analysis title	CMH ESTIMATE OF COMMON ODDS RATIO
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV

Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0144
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.9

Statistical analysis title	DIFFERENCE OF DRUG-RELATED GRADE 3-5 AE RATES
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Estimated Difference of rates
Point estimate	-12.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.7
upper limit	-2.6

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR) ^[2]
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End point description:

The percentage of participants with a best overall response (BOR) of complete response (CR) or partial response (PR). BOR is defined as the best response, as determined by the investigator, recorded between the date of randomization and the date of progression per RECIST 1.1 or the date of subsequent anticancer therapy, whichever occurred first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled at Week 12 following randomization, every 8 weeks for the first 12 months and then every 12 weeks until disease progression. Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

End point type	Secondary
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End point timeframe:

From date of randomization to date of objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first (up to approximately 5 years)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: Percentage of participants				
number (confidence interval 95%)	47.8 (40.3 to 55.3)	53.4 (45.8 to 60.9)		

Statistical analyses

Statistical analysis title	CMH ESTIMATE OF COMMON ODDS RATIO
Statistical analysis description:	
Estimate of NIVO 3 + IPI 1- NIVO 1 + IPI 3 is based on Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for PD-L1 expression and M stage at screening as entered into the IVRS.	
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2923
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.21

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS) ^[3]
End point description:	
The time between the date of randomization and the date of death due to any cause. A participant who has not died will be censored at the last known alive date. OS will be followed continuously while participants are on the study drug and every 3 months via in-person or phone contact after participants discontinue the study drug. Based on Kaplan-Meier Estimates. Note: 99999 = N/A due to insufficient number of participants with events.	
End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression or date of death from any cause, whichever came first (up to approximately 5 years)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: Months				
median (confidence interval 95%)	99999 (43.73 to 99999)	99999 (40.84 to 99999)		

Statistical analyses

Statistical analysis title	Hazard Ratio of NIVO 3 + IPI 1 over NIVO 1 + IPI 3
Statistical analysis description: Stratified Cox proportional hazard model. Hazard Ratio is NIVO 3 + IPI 1 over NIVO 1 + IPI 3.	
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.47

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS) ^[4]
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End point description:

The time between the date of randomization and the first date of documented progression, determined by the investigator, or death due to any cause, whichever occurs first. Participants who die without a reported progression will be considered to have progressed on the date of their death. Those who did not progress or die will be censored on the date of their last evaluable tumor assessment. Participants without on study tumor assessments and who did not die will be censored on their date of randomization. Participants who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy. Progression is defined as at least a 20% increase in the sum of diameters of target lesions or the appearance of one or more new lesions. The sum must also demonstrate an absolute increase of at least 5 mm. (Based on Kaplan-Meier Estimates)

End point type	Secondary
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End point timeframe:

From randomization to the first date of documented progression or death due to any cause, whichever occurs first (up to approximately 5 years)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: Months				
median (confidence interval 95%)	10.18 (6.24 to 21.91)	9.99 (6.28 to 28.88)		

Statistical analyses

Statistical analysis title	Hazard Ratio NIVO 3 + IPI 1 over NIVO 1 + IPI 3
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4512
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.48

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Physical Functioning Scale

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Physical Functioning Scale ^[5]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Physical Functioning sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	-2.1 (± 16.2)	-4.9 (± 16.5)		
Week 16	-1.9 (± 15.3)	-2.7 (± 15.8)		
Week 20	-1.4 (± 10.7)	-2.7 (± 13.7)		
Week 24	-5.1 (± 15.6)	-5.7 (± 13.6)		
Week 28	-2.5 (± 15.0)	-0.7 (± 14.8)		
Week 32	-3.3 (± 16.5)	-3.5 (± 15.4)		
Week 36	-4.0 (± 19.1)	-2.9 (± 14.8)		
Week 40	-3.3 (± 17.3)	-3.4 (± 16.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Role Functioning Scale

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Role Functioning Scale ^[6]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Role Functioning sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	-2.5 (± 28.3)	-8.8 (± 25.6)		
Week 16	-6.6 (± 30.3)	2.1 (± 25.6)		
Week 20	-1.8 (± 19.9)	-5.2 (± 25.2)		
Week 24	-3.9 (± 19.9)	-9.8 (± 29.3)		

Week 28	-0.9 (± 23.4)	-1.3 (± 26.0)		
Week 32	-3.6 (± 25.1)	-2.2 (± 29.3)		
Week 36	-3.9 (± 26.4)	-2.9 (± 30.5)		
Week 40	-4.0 (± 26.7)	-5.2 (± 34.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Emotional Functioning Scale

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Emotional Functioning Scale ^[7]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Emotional Functioning sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	4.5 (± 17.9)	4.4 (± 16.8)		
Week 16	0.0 (± 21.7)	6.6 (± 20.1)		
Week 20	3.9 (± 18.0)	4.5 (± 18.0)		
Week 24	3.4 (± 18.4)	2.6 (± 23.3)		
Week 28	5.9 (± 19.5)	5.6 (± 22.5)		
Week 32	5.5 (± 17.3)	5.1 (± 21.6)		
Week 36	3.0 (± 17.0)	4.7 (± 22.0)		
Week 40	4.5 (± 21.4)	5.4 (± 19.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Cognitive Functioning Scale

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Cognitive Functioning Scale ^[8]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Cognitive Functioning sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	-3.4 (± 15.0)	-1.9 (± 16.7)		
Week 16	-2.6 (± 14.4)	-5.9 (± 22.4)		
Week 20	-1.9 (± 16.9)	-6.0 (± 17.6)		
Week 24	-2.7 (± 15.0)	-3.4 (± 14.9)		
Week 28	-3.7 (± 17.7)	-3.7 (± 16.8)		
Week 32	-1.5 (± 16.6)	-4.8 (± 16.9)		
Week 36	-3.1 (± 18.5)	-8.8 (± 20.6)		
Week 40	-2.6 (± 20.3)	-4.4 (± 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Social Functioning Scale

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Social Functioning Scale ^[9]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Social Functioning sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	110		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	-3.1 (± 22.8)	-6.1 (± 25.0)		
Week 16	-6.3 (± 23.5)	-2.8 (± 26.7)		
Week 20	-4.6 (± 21.0)	-3.2 (± 20.5)		
Week 24	-1.6 (± 17.2)	-3.7 (± 20.0)		
Week 28	1.4 (± 18.1)	-1.0 (± 22.2)		
Week 32	0.3 (± 17.6)	-1.0 (± 19.6)		
Week 36	0.5 (± 20.4)	0.3 (± 22.7)		
Week 40	1.1 (± 22.0)	-4.1 (± 23.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Global Health Status

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Global Health Status ^[10]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 comprises 6 functional scales (role function, physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). 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
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	111		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	0.5 (± 22.9)	-0.5 (± 19.0)		
Week 16	0.0 (± 18.5)	5.0 (± 24.5)		
Week 20	-1.5 (± 19.9)	0.0 (± 19.1)		
Week 24	-0.5 (± 16.1)	-1.6 (± 24.9)		
Week 28	0.7 (± 21.1)	6.3 (± 23.4)		
Week 32	-0.5 (± 23.2)	5.4 (± 23.9)		
Week 36	-2.9 (± 21.8)	2.6 (± 25.6)		
Week 40	-0.8 (± 22.2)	3.7 (± 21.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Dyspnea

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Dyspnea ^[11]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Dyspnea sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	4.4 (± 21.5)	6.3 (± 23.0)		
Week 16	5.8 (± 22.0)	2.1 (± 21.1)		
Week 20	2.7 (± 22.7)	2.3 (± 22.4)		
Week 24	2.3 (± 19.5)	2.3 (± 22.4)		

Week 28	3.2 (± 25.7)	0.0 (± 23.3)		
Week 32	2.6 (± 23.1)	2.6 (± 22.7)		
Week 36	4.2 (± 21.8)	0.0 (± 21.1)		
Week 40	3.7 (± 22.5)	2.2 (± 21.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Insomnia

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Insomnia ^[12]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Insomnia sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	0.6 (± 28.7)	-1.5 (± 30.5)		
Week 16	-0.5 (± 28.0)	-2.8 (± 29.0)		
Week 20	-0.9 (± 28.5)	-6.3 (± 28.9)		
Week 24	2.3 (± 28.0)	-7.5 (± 26.5)		
Week 28	0.9 (± 25.6)	-7.3 (± 28.0)		
Week 32	-3.1 (± 24.1)	-10.5 (± 29.4)		
Week 36	0.5 (± 24.8)	-8.5 (± 30.4)		
Week 40	-1.1 (± 18.9)	-14.1 (± 31.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Appetite Loss

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Appetite Loss ^[13]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Appetite loss sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	3.0 (± 24.7)	4.8 (± 28.6)		
Week 16	2.1 (± 28.6)	-1.4 (± 31.5)		
Week 20	1.4 (± 21.8)	-3.5 (± 25.7)		
Week 24	-0.9 (± 22.9)	-2.9 (± 32.0)		
Week 28	-0.9 (± 23.0)	-7.3 (± 26.3)		
Week 32	1.0 (± 27.6)	-7.7 (± 23.4)		
Week 36	-2.6 (± 24.7)	-9.2 (± 26.7)		
Week 40	-2.6 (± 22.6)	-6.7 (± 31.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Constipation

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Constipation ^[14]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Constipation sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	0.3 (± 26.4)	2.4 (± 26.7)		
Week 16	5.3 (± 22.6)	-2.8 (± 32.1)		
Week 20	3.7 (± 26.4)	1.1 (± 25.7)		
Week 24	-0.5 (± 23.2)	-1.7 (± 26.8)		
Week 28	3.2 (± 27.5)	1.4 (± 28.8)		
Week 32	2.6 (± 23.1)	-5.1 (± 27.5)		
Week 36	3.7 (± 23.3)	-0.7 (± 29.4)		
Week 40	1.1 (± 21.6)	0.7 (± 29.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Diarrhea

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Diarrhea ^[15]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Diarrhea sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	1.4 (± 18.5)	1.2 (± 23.6)		
Week 16	8.5 (± 22.4)	2.8 (± 30.6)		
Week 20	2.3 (± 19.6)	-1.7 (± 22.0)		
Week 24	1.8 (± 17.5)	1.1 (± 25.7)		
Week 28	2.8 (± 19.2)	0.0 (± 19.4)		
Week 32	0.5 (± 19.1)	-2.6 (± 21.7)		
Week 36	3.6 (± 16.9)	-2.0 (± 20.5)		
Week 40	-0.5 (± 18.4)	-3.7 (± 16.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Financial Difficulties

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Financial Difficulties ^[16]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Financial difficulties sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	109		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	2.0 (± 24.4)	2.4 (± 22.5)		
Week 16	1.1 (± 19.8)	4.9 (± 21.7)		
Week 20	2.8 (± 20.7)	5.3 (± 19.7)		

Week 24	1.8 (± 22.8)	5.7 (± 17.8)		
Week 28	2.8 (± 23.6)	6.8 (± 22.5)		
Week 32	2.1 (± 22.7)	5.8 (± 22.6)		
Week 36	3.6 (± 22.3)	8.5 (± 18.7)		
Week 40	1.1 (± 23.9)	8.1 (± 19.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Fatigue

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Fatigue ^[17]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Fatigue sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	5.1 (± 23.3)	11.5 (± 23.2)		
Week 16	9.2 (± 25.8)	5.1 (± 24.4)		
Week 20	4.4 (± 20.6)	7.9 (± 20.5)		
Week 24	5.4 (± 20.5)	6.9 (± 24.3)		
Week 28	4.8 (± 22.9)	2.1 (± 19.5)		
Week 32	5.5 (± 23.7)	3.2 (± 22.9)		
Week 36	5.4 (± 27.1)	1.7 (± 21.2)		
Week 40	5.8 (± 24.3)	0.7 (± 24.7)		

Statistical analyses

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Nausea and Vomiting

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Nausea and Vomiting ^[18]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Nausea and Vomiting sub-scale 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 indicate a higher level of symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	112		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	1.5 (± 16.4)	4.9 (± 18.3)		
Week 16	-0.3 (± 20.4)	3.1 (± 11.7)		
Week 20	-2.3 (± 10.1)	1.1 (± 13.9)		
Week 24	-0.5 (± 16.2)	4.0 (± 18.0)		
Week 28	0.7 (± 13.5)	0.7 (± 14.3)		
Week 32	-1.3 (± 14.2)	0.3 (± 15.7)		
Week 36	0.0 (± 18.5)	1.6 (± 16.1)		
Week 40	-1.3 (± 12.1)	0.7 (± 12.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Pain

End point title	Mean Changes from Baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-30) Pain ^[19]
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End point description:

Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire. The Pain sub-scale 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 indicate a higher level of

symptoms; lower scores indicating lesser burden and improved symptoms or quality of life. A clinically meaningful change in score may be regarded as 10 points.

End point type	Secondary
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End point timeframe:

Weeks 7, 16, 20, 24, 28, 32, 36, 40

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the Outcome Measures module

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	111		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Week 7	-1.7 (± 28.0)	1.5 (± 25.6)		
Week 16	-2.9 (± 22.9)	-2.8 (± 23.4)		
Week 20	-5.7 (± 20.1)	1.7 (± 28.0)		
Week 24	-2.9 (± 20.9)	0.9 (± 31.9)		
Week 28	-3.0 (± 25.5)	-3.7 (± 30.9)		
Week 32	-2.8 (± 27.1)	-4.5 (± 26.0)		
Week 36	-2.6 (± 21.3)	-2.6 (± 29.9)		
Week 40	0.3 (± 25.3)	-3.3 (± 27.2)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: The Percentage of Participants with Drug-Related Grade 3 - 5 Adverse Events (AEs) - Extended Collection

End point title	The Percentage of Participants with Drug-Related Grade 3 - 5 Adverse Events (AEs) - Extended Collection ^[20]
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End point description:

The percentage of participants who experienced at least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment. AE grade was defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.

Note: This outcome measure represents an updated version of the primary endpoint to include additional data collection that has occurred after the primary completion date. (Assessments were made until study completion date: 28-May-2021)

End point type	Post-hoc
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End point timeframe:

From first dose of study treatment to 30 days after the last dose of study treatment (up to approximately 30 months)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Cohort C/N6I1 assessed for exploratory outcome measures only and not reported in the

End point values	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV	Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	178		
Units: Percentage of participants				
number (confidence interval 95%)	33.9 (27.0 to 41.3)	48.3 (40.8 to 55.9)		

Statistical analyses

Statistical analysis title	DIFFERENCE OF DRUG-RELATED GRADE 3-5 AE RATES
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Estimated Difference of rates
Point estimate	-14.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.5
upper limit	-4.3

Statistical analysis title	CMH ESTIMATE OF COMMON ODDS RATIO
Statistical analysis description:	
Estimate of NIVO 3 + IPI 1- NIVO 1 + IPI 3 is based on Cochran-Mantel-Haenszel (CMH) method of weighting, adjusting for PD-L1 expression and M stage at screening as entered into the IVRS.	
Comparison groups	Nivolumab 3 mg/kg IV + Ipilimumab 1 mg/kg IV v Ipilimumab 3 mg/kg IV + Nivolumab 1 mg/kg IV
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0059
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.84

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs/SAEs are collected from the first dose date until the last dose date + 30 days (Up to approximately 30 months) Participants were assessed for All Cause Mortality from their first dose until the study was completed (up to approximately 5 years)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24
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Reporting groups

Reporting group title	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg
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Reporting group description:

nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks

Reporting group title	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg
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Reporting group description:

nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg IV every 3 weeks for 4 doses then nivolumab (flat dose 480 mg) every 4 weeks.

Reporting group title	Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
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Reporting group description:

nivolumab 6 mg/kg plus ipilimumab 1 mg/kg followed by nivolumab 480 mg Flat Dose 4 weeks later and repeated every 8 weeks

Serious adverse events	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	127 / 178 (71.35%)	109 / 180 (60.56%)	14 / 27 (51.85%)
number of deaths (all causes)	78	85	15
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Malignant neoplasm progression			

subjects affected / exposed	26 / 178 (14.61%)	23 / 180 (12.78%)	3 / 27 (11.11%)
occurrences causally related to treatment / all	3 / 28	1 / 25	0 / 3
deaths causally related to treatment / all	1 / 14	0 / 13	0 / 1
Metastases to central nervous system			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Squamous cell carcinoma			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Tumour pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Superior vena cava syndrome			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Vasculitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Aortic stenosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Shock haemorrhagic			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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			
Chest discomfort			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Chest pain			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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 physical health deterioration			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Inflammation			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Influenza like illness			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Pain			
subjects affected / exposed	3 / 178 (1.69%)	1 / 180 (0.56%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	11 / 178 (6.18%)	5 / 180 (2.78%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	7 / 13	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Hyperthermia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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 system disorders			
Cytokine release syndrome			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Sarcoidosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Hypersensitivity			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Cough			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Dyspnoea			

subjects affected / exposed	2 / 178 (1.12%)	1 / 180 (0.56%)	0 / 27 (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
Haemothorax			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Interstitial lung disease			
subjects affected / exposed	1 / 178 (0.56%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Lung disorder			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Organising pneumonia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Pleural effusion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Pleurisy			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Pneumonitis			

subjects affected / exposed	1 / 178 (0.56%)	7 / 180 (3.89%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	5 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	4 / 178 (2.25%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sarcoidosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Respiratory distress			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Bronchial obstruction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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			
Mental status changes			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Mania			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Blood bilirubin increased			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Hepatic enzyme increased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Influenza A virus test positive			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Lipase increased			
subjects affected / exposed	0 / 178 (0.00%)	3 / 180 (1.67%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	4 / 178 (2.25%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Antibiotic level below therapeutic			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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 physical condition abnormal			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Overdose			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Rib fracture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Angina pectoris			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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 fibrillation			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Myocarditis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Tachycardia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Cardiopulmonary failure			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Immune-mediated myocarditis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Dystonia			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Epilepsy			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Headache			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Hyperaesthesia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Meningism			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningoradiculitis			

subjects affected / exposed	3 / 178 (1.69%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Motor dysfunction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Paraesthesia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Partial seizures			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Sciatica			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Spinal cord compression			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Status epilepticus			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 178 (1.12%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	4 / 6	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Febrile neutropenia			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Haemolysis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Lymph node pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Eye disorders			

Diplopia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Dry eye			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Keratitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Orbital myositis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vision blurred			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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 disorders			
Abdominal pain			
subjects affected / exposed	2 / 178 (1.12%)	2 / 180 (1.11%)	0 / 27 (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
Autoimmune colitis			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	10 / 178 (5.62%)	6 / 180 (3.33%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	11 / 11	5 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	12 / 178 (6.74%)	5 / 180 (2.78%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	13 / 14	5 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dry mouth			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Dysphagia			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Gastritis			
subjects affected / exposed	2 / 178 (1.12%)	1 / 180 (0.56%)	0 / 27 (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
Gastrointestinal necrosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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 perforation			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 178 (0.00%)	3 / 180 (1.67%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nausea			

subjects affected / exposed	3 / 178 (1.69%)	3 / 180 (1.67%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 178 (0.56%)	3 / 180 (1.67%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 178 (2.25%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Colitis ulcerative			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Immune-mediated enterocolitis			
subjects affected / exposed	2 / 178 (1.12%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	5 / 178 (2.81%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	6 / 6	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Hepatitis			
subjects affected / exposed	8 / 178 (4.49%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	8 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	1 / 178 (0.56%)	3 / 180 (1.67%)	0 / 27 (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
Hypertransaminasaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Hepatic cytolysis			
subjects affected / exposed	4 / 178 (2.25%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis acute			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pemphigoid			

subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Rash			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Toxic skin eruption			
subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune nephritis			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Renal failure			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Chronic kidney disease			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Nephritis			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	3 / 178 (1.69%)	1 / 180 (0.56%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	2 / 3	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adrenocorticotrophic hormone deficiency			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Hyperthyroidism			
subjects affected / exposed	3 / 178 (1.69%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypophysitis			
subjects affected / exposed	6 / 178 (3.37%)	2 / 180 (1.11%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	6 / 6	2 / 2	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypopituitarism			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroiditis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Glucocorticoid deficiency			

subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Back pain			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Fasciitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Myalgia			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (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
Rhabdomyolysis			

subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Infections and infestations			
Arthritis bacterial			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Bronchitis			
subjects affected / exposed	1 / 178 (0.56%)	2 / 180 (1.11%)	0 / 27 (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
Cellulitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Chorioretinitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Diverticulitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Endocarditis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Erysipelas			

subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Infected cyst			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Lymph gland infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Meningoencephalitis viral			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 178 (2.25%)	5 / 180 (2.78%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Sepsis			
subjects affected / exposed	3 / 178 (1.69%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Spinal cord infection			
subjects affected / exposed	0 / 178 (0.00%)	3 / 180 (1.67%)	0 / 27 (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
Urinary tract infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Diverticulitis intestinal perforated			
subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Folliculitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Pneumonia pneumococcal			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (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 ketoacidosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 178 (1.12%)	0 / 180 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 178 (0.00%)	1 / 180 (0.56%)	0 / 27 (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
Hyponatraemia			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	0 / 27 (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
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 178 (0.56%)	2 / 180 (1.11%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	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 1 mg/kg + Ipilimumab 3 mg/kg	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 178 (96.63%)	169 / 180 (93.89%)	26 / 27 (96.30%)
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 178 (3.37%)	9 / 180 (5.00%)	3 / 27 (11.11%)
occurrences (all)	6	9	3
Lymphoedema			
subjects affected / exposed	2 / 178 (1.12%)	5 / 180 (2.78%)	2 / 27 (7.41%)
occurrences (all)	2	6	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	54 / 178 (30.34%)	49 / 180 (27.22%)	8 / 27 (29.63%)
occurrences (all)	67	66	11
Chills			
subjects affected / exposed	10 / 178 (5.62%)	12 / 180 (6.67%)	3 / 27 (11.11%)
occurrences (all)	12	13	3
Fatigue			
subjects affected / exposed	51 / 178 (28.65%)	66 / 180 (36.67%)	8 / 27 (29.63%)
occurrences (all)	57	76	9

Mucosal inflammation subjects affected / exposed occurrences (all)	6 / 178 (3.37%) 8	2 / 180 (1.11%) 2	2 / 27 (7.41%) 3
Influenza like illness subjects affected / exposed occurrences (all)	15 / 178 (8.43%) 18	14 / 180 (7.78%) 19	1 / 27 (3.70%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	12 / 178 (6.74%) 13	18 / 180 (10.00%) 19	2 / 27 (7.41%) 3
Pyrexia subjects affected / exposed occurrences (all)	47 / 178 (26.40%) 69	39 / 180 (21.67%) 53	6 / 27 (22.22%) 6
Reproductive system and breast disorders Vulvovaginal pruritus subjects affected / exposed occurrences (all)	0 / 178 (0.00%) 0	0 / 180 (0.00%) 0	2 / 27 (7.41%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	35 / 178 (19.66%) 45	38 / 180 (21.11%) 45	6 / 27 (22.22%) 8
Dyspnoea subjects affected / exposed occurrences (all)	26 / 178 (14.61%) 29	33 / 180 (18.33%) 38	1 / 27 (3.70%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	1 / 180 (0.56%) 1	3 / 27 (11.11%) 3
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	18 / 178 (10.11%) 19	24 / 180 (13.33%) 28	0 / 27 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	7 / 178 (3.93%) 7	7 / 180 (3.89%) 8	2 / 27 (7.41%) 3
Investigations Alanine aminotransferase increased			

subjects affected / exposed	36 / 178 (20.22%)	22 / 180 (12.22%)	6 / 27 (22.22%)
occurrences (all)	47	25	9
Amylase increased			
subjects affected / exposed	14 / 178 (7.87%)	16 / 180 (8.89%)	4 / 27 (14.81%)
occurrences (all)	15	21	4
Aspartate aminotransferase increased			
subjects affected / exposed	30 / 178 (16.85%)	18 / 180 (10.00%)	5 / 27 (18.52%)
occurrences (all)	38	20	6
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 178 (1.69%)	10 / 180 (5.56%)	2 / 27 (7.41%)
occurrences (all)	3	12	3
Blood cholesterol increased			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	2 / 27 (7.41%)
occurrences (all)	1	2	6
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 178 (1.69%)	7 / 180 (3.89%)	3 / 27 (11.11%)
occurrences (all)	5	7	3
Blood creatinine increased			
subjects affected / exposed	12 / 178 (6.74%)	6 / 180 (3.33%)	2 / 27 (7.41%)
occurrences (all)	12	7	5
Blood thyroid stimulating hormone increased			
subjects affected / exposed	2 / 178 (1.12%)	5 / 180 (2.78%)	4 / 27 (14.81%)
occurrences (all)	2	6	7
Cortisol decreased			
subjects affected / exposed	0 / 178 (0.00%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	0	3	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 178 (4.49%)	13 / 180 (7.22%)	1 / 27 (3.70%)
occurrences (all)	9	15	1
Haemoglobin decreased			
subjects affected / exposed	1 / 178 (0.56%)	1 / 180 (0.56%)	2 / 27 (7.41%)
occurrences (all)	1	1	5
Lipase increased			

subjects affected / exposed	20 / 178 (11.24%)	17 / 180 (9.44%)	3 / 27 (11.11%)
occurrences (all)	25	23	5
Neutrophil count decreased			
subjects affected / exposed	2 / 178 (1.12%)	1 / 180 (0.56%)	2 / 27 (7.41%)
occurrences (all)	3	4	5
Weight decreased			
subjects affected / exposed	29 / 178 (16.29%)	25 / 180 (13.89%)	1 / 27 (3.70%)
occurrences (all)	31	25	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 178 (0.56%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	1	4	3
Blood magnesium decreased			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Protein total decreased			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	2 / 27 (7.41%)
occurrences (all)	1	0	2
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	5 / 178 (2.81%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	5	5	2
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 178 (5.06%)	9 / 180 (5.00%)	6 / 27 (22.22%)
occurrences (all)	11	9	6
Headache			
subjects affected / exposed	51 / 178 (28.65%)	38 / 180 (21.11%)	4 / 27 (14.81%)
occurrences (all)	76	53	4
Paraesthesia			
subjects affected / exposed	16 / 178 (8.99%)	9 / 180 (5.00%)	1 / 27 (3.70%)
occurrences (all)	18	10	1
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	17 / 178 (9.55%)	20 / 180 (11.11%)	4 / 27 (14.81%)
occurrences (all)	19	24	4
Neutropenia			
subjects affected / exposed	3 / 178 (1.69%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	3	3	2
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 178 (0.56%)	0 / 180 (0.00%)	3 / 27 (11.11%)
occurrences (all)	1	0	3
Eye disorders			
Vision blurred			
subjects affected / exposed	9 / 178 (5.06%)	6 / 180 (3.33%)	1 / 27 (3.70%)
occurrences (all)	9	9	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	25 / 178 (14.04%)	36 / 180 (20.00%)	6 / 27 (22.22%)
occurrences (all)	32	47	7
Abdominal pain upper			
subjects affected / exposed	16 / 178 (8.99%)	12 / 180 (6.67%)	2 / 27 (7.41%)
occurrences (all)	17	15	2
Constipation			
subjects affected / exposed	31 / 178 (17.42%)	25 / 180 (13.89%)	3 / 27 (11.11%)
occurrences (all)	37	26	3
Diarrhoea			
subjects affected / exposed	73 / 178 (41.01%)	66 / 180 (36.67%)	11 / 27 (40.74%)
occurrences (all)	117	125	16
Dry mouth			
subjects affected / exposed	28 / 178 (15.73%)	16 / 180 (8.89%)	3 / 27 (11.11%)
occurrences (all)	30	17	4
Nausea			
subjects affected / exposed	49 / 178 (27.53%)	41 / 180 (22.78%)	9 / 27 (33.33%)
occurrences (all)	77	59	10
Vomiting			
subjects affected / exposed	34 / 178 (19.10%)	28 / 180 (15.56%)	4 / 27 (14.81%)
occurrences (all)	49	40	6
Abdominal distension			

subjects affected / exposed occurrences (all)	2 / 178 (1.12%) 2	4 / 180 (2.22%) 5	2 / 27 (7.41%) 2
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	4 / 178 (2.25%)	1 / 180 (0.56%)	2 / 27 (7.41%)
occurrences (all)	4	1	2
Hepatic cytolysis			
subjects affected / exposed	6 / 178 (3.37%)	6 / 180 (3.33%)	3 / 27 (11.11%)
occurrences (all)	6	6	3
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	11 / 178 (6.18%)	8 / 180 (4.44%)	0 / 27 (0.00%)
occurrences (all)	11	8	0
Eczema			
subjects affected / exposed	3 / 178 (1.69%)	4 / 180 (2.22%)	4 / 27 (14.81%)
occurrences (all)	3	4	5
Intertrigo			
subjects affected / exposed	1 / 178 (0.56%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	1	3	2
Night sweats			
subjects affected / exposed	6 / 178 (3.37%)	4 / 180 (2.22%)	2 / 27 (7.41%)
occurrences (all)	7	5	2
Pruritus			
subjects affected / exposed	60 / 178 (33.71%)	55 / 180 (30.56%)	13 / 27 (48.15%)
occurrences (all)	79	69	18
Rash			
subjects affected / exposed	54 / 178 (30.34%)	42 / 180 (23.33%)	0 / 27 (0.00%)
occurrences (all)	69	51	0
Rash macular			
subjects affected / exposed	8 / 178 (4.49%)	7 / 180 (3.89%)	2 / 27 (7.41%)
occurrences (all)	8	7	2
Rash maculo-papular			
subjects affected / exposed	17 / 178 (9.55%)	10 / 180 (5.56%)	5 / 27 (18.52%)
occurrences (all)	18	13	5
Skin hypopigmentation			

subjects affected / exposed	0 / 178 (0.00%)	2 / 180 (1.11%)	2 / 27 (7.41%)
occurrences (all)	0	2	2
Vitiligo			
subjects affected / exposed	16 / 178 (8.99%)	21 / 180 (11.67%)	3 / 27 (11.11%)
occurrences (all)	16	21	3
Rash erythematous			
subjects affected / exposed	0 / 178 (0.00%)	0 / 180 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Erythema			
subjects affected / exposed	5 / 178 (2.81%)	7 / 180 (3.89%)	2 / 27 (7.41%)
occurrences (all)	5	8	2
Rash papular			
subjects affected / exposed	3 / 178 (1.69%)	2 / 180 (1.11%)	2 / 27 (7.41%)
occurrences (all)	3	2	2
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 178 (0.56%)	3 / 180 (1.67%)	2 / 27 (7.41%)
occurrences (all)	1	3	3
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	12 / 178 (6.74%)	4 / 180 (2.22%)	1 / 27 (3.70%)
occurrences (all)	12	4	1
Hyperthyroidism			
subjects affected / exposed	31 / 178 (17.42%)	20 / 180 (11.11%)	3 / 27 (11.11%)
occurrences (all)	31	22	3
Hypophysitis			
subjects affected / exposed	12 / 178 (6.74%)	10 / 180 (5.56%)	3 / 27 (11.11%)
occurrences (all)	13	10	3
Hypothyroidism			
subjects affected / exposed	41 / 178 (23.03%)	27 / 180 (15.00%)	2 / 27 (7.41%)
occurrences (all)	41	27	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 178 (20.22%)	39 / 180 (21.67%)	6 / 27 (22.22%)
occurrences (all)	41	50	7
Myalgia			

subjects affected / exposed	15 / 178 (8.43%)	23 / 180 (12.78%)	3 / 27 (11.11%)
occurrences (all)	22	26	3
Back pain			
subjects affected / exposed	23 / 178 (12.92%)	14 / 180 (7.78%)	4 / 27 (14.81%)
occurrences (all)	29	16	6
Pain in extremity			
subjects affected / exposed	16 / 178 (8.99%)	15 / 180 (8.33%)	5 / 27 (18.52%)
occurrences (all)	16	17	8
Muscle spasms			
subjects affected / exposed	10 / 178 (5.62%)	7 / 180 (3.89%)	0 / 27 (0.00%)
occurrences (all)	11	7	0
Muscular weakness			
subjects affected / exposed	7 / 178 (3.93%)	4 / 180 (2.22%)	2 / 27 (7.41%)
occurrences (all)	7	5	2
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 178 (8.99%)	16 / 180 (8.89%)	5 / 27 (18.52%)
occurrences (all)	20	23	5
Upper respiratory tract infection			
subjects affected / exposed	8 / 178 (4.49%)	14 / 180 (7.78%)	1 / 27 (3.70%)
occurrences (all)	12	19	2
Urinary tract infection			
subjects affected / exposed	13 / 178 (7.30%)	5 / 180 (2.78%)	1 / 27 (3.70%)
occurrences (all)	18	5	2
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 178 (17.42%)	37 / 180 (20.56%)	4 / 27 (14.81%)
occurrences (all)	34	43	4
Dehydration			
subjects affected / exposed	5 / 178 (2.81%)	2 / 180 (1.11%)	2 / 27 (7.41%)
occurrences (all)	5	2	2
Hypokalaemia			
subjects affected / exposed	17 / 178 (9.55%)	15 / 180 (8.33%)	1 / 27 (3.70%)
occurrences (all)	22	19	1
Hyponatraemia			

subjects affected / exposed	9 / 178 (5.06%)	5 / 180 (2.78%)	0 / 27 (0.00%)
occurrences (all)	9	6	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 January 2016	The interval between the end of Part 1 and the beginning of Part 2 has been amended from 3 to 6 weeks. The simultaneous administration of the nivolumab and ipilimumab regimen planned in Part 1 of the treatment phase has been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported