



## 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-naive 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:

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**Subjects enrolled per age group**

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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

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## 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
<b>Arm title</b>	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

<b>Arm title</b>	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	
<b>Arm title</b>	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

<b>Number of subjects in period 1</b>	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) <sup>[1]</sup>
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

<b>Statistical analysis title</b>	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) <sup>[2]</sup>
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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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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) <sup>[3]</sup>
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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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) <sup>[4]</sup>
End point description:	
<p>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)</p>	
End point type	Secondary
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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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 <sup>[5]</sup>
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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

<b>End point values</b>	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 <sup>[6]</sup>
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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

<b>End point values</b>	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 <sup>[7]</sup>
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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 <sup>[8]</sup>
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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 <sup>[9]</sup>
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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

<b>End point values</b>	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 <sup>[10]</sup>
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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

<b>End point values</b>	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 <sup>[11]</sup>
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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

<b>End point values</b>	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 <sup>[12]</sup>
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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 <sup>[13]</sup>
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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 <sup>[14]</sup>
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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

<b>End point values</b>	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 <sup>[15]</sup>
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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

<b>End point values</b>	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 <sup>[16]</sup>
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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

<b>End point values</b>	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 <sup>[17]</sup>
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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

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) 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 <sup>[18]</sup>
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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 <sup>[19]</sup>
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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 <sup>[20]</sup>
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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

<b>End point values</b>	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

<b>Statistical analysis title</b>	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

<b>Statistical analysis title</b>	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
Dictionary version	24

### 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

<b>Serious adverse events</b>	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
<b>Metastases to central nervous system</b>			
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
<b>Metastases to lung</b>			
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
<b>Squamous cell carcinoma</b>			
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
<b>Tumour haemorrhage</b>			
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
<b>Tumour pain</b>			
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
<b>Metastatic malignant melanoma</b>			
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
<b>Vascular disorders</b>			
<b>Deep vein thrombosis</b>			
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
<b>Superior vena cava syndrome</b>			

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
<b>Sarcoidosis</b>			
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
<b>Hypersensitivity</b>			
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
<b>Reproductive system and breast disorders</b>			
<b>Pelvic pain</b>			
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
<b>Ovarian cyst</b>			
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
<b>Respiratory, thoracic and mediastinal disorders</b>			
<b>Chronic obstructive pulmonary disease</b>			
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
<b>Cough</b>			
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
<b>Dyspnoea</b>			

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
<b>Haemothorax</b>			
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
<b>Interstitial lung disease</b>			
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
<b>Lower respiratory tract congestion</b>			
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
<b>Lung disorder</b>			
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
<b>Organising pneumonia</b>			
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
<b>Pleural effusion</b>			
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
<b>Pleurisy</b>			
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
<b>Pneumonitis</b>			

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
<b>Pneumothorax</b>			
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
<b>Pulmonary embolism</b>			
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
<b>Pulmonary sarcoidosis</b>			
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
<b>Respiratory distress</b>			
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
<b>Bronchial obstruction</b>			
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
<b>Pulmonary mass</b>			
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
<b>Psychiatric disorders</b>			
<b>Mental status changes</b>			
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
<b>Mania</b>			

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
<b>Investigations</b>			
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
<b>Injury, poisoning and procedural complications</b>			
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
<b>Cardiac disorders</b>			
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
<b>Epilepsy</b>			
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
<b>Haemorrhage intracranial</b>			
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
<b>Headache</b>			
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
<b>Hyperaesthesia</b>			
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
<b>Ischaemic stroke</b>			
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
<b>Loss of consciousness</b>			
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
<b>Meningism</b>			
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
<b>Meningoradiculitis</b>			

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
<b>Migraine</b>			
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
<b>Motor dysfunction</b>			
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
<b>Paraesthesia</b>			
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
<b>Partial seizures</b>			
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
<b>Peripheral sensory neuropathy</b>			
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
<b>Sciatica</b>			
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
<b>Seizure</b>			
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
<b>Spinal cord compression</b>			

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
<b>Pancreatitis</b>			
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
<b>Small intestinal obstruction</b>			
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
<b>Vomiting</b>			
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
<b>Ascites</b>			
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
<b>Colitis ulcerative</b>			
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
<b>Immune-mediated enterocolitis</b>			
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
<b>Hepatobiliary disorders</b>			
<b>Autoimmune hepatitis</b>			
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
<b>Cholecystitis</b>			

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
<b>Rash</b>			
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
<b>Urticaria</b>			
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
<b>Toxic skin eruption</b>			
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
<b>Renal and urinary disorders</b>			
<b>Acute kidney injury</b>			
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
<b>Autoimmune nephritis</b>			
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
<b>Renal failure</b>			
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
<b>Chronic kidney disease</b>			
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
<b>Nephritis</b>			

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
<b>Endocrine disorders</b>			
<b>Adrenal insufficiency</b>			
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
<b>Adrenocorticotrophic hormone deficiency</b>			
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
<b>Hyperthyroidism</b>			
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
<b>Hypophysitis</b>			
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
<b>Hypopituitarism</b>			
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
<b>Thyroiditis</b>			
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
<b>Adrenocortical insufficiency acute</b>			
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
<b>Glucocorticoid deficiency</b>			

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
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Arthralgia</b>			
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
<b>Back pain</b>			
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
<b>Bone pain</b>			
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
<b>Fasciitis</b>			
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
<b>Myalgia</b>			
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
<b>Myositis</b>			
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
<b>Pain in extremity</b>			
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
<b>Rhabdomyolysis</b>			

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
<b>Infected cyst</b>			
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
<b>Influenza</b>			
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
<b>Lymph gland infection</b>			
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
<b>Meningoencephalitis viral</b>			
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
<b>Pneumonia</b>			
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
<b>Respiratory tract infection</b>			
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
<b>Sepsis</b>			
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
<b>Septic shock</b>			

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
<b>Pneumonia pneumococcal</b>			
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
<b>Pneumonia respiratory syncytial viral</b>			
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
<b>Pyelonephritis</b>			
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
<b>Metabolism and nutrition disorders</b>			
<b>Decreased appetite</b>			
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
<b>Diabetic ketoacidosis</b>			
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
<b>Hypercalcaemia</b>			
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
<b>Hyperglycaemia</b>			
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
<b>Hypokalaemia</b>			

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 %

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

Anaemia subjects affected / exposed occurrences (all)	17 / 178 (9.55%) 19	20 / 180 (11.11%) 24	4 / 27 (14.81%) 4
Neutropenia subjects affected / exposed occurrences (all)	3 / 178 (1.69%) 3	3 / 180 (1.67%) 3	2 / 27 (7.41%) 2
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	0 / 180 (0.00%) 0	3 / 27 (11.11%) 3
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	9 / 178 (5.06%) 9	6 / 180 (3.33%) 9	1 / 27 (3.70%) 1
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	25 / 178 (14.04%) 32	36 / 180 (20.00%) 47	6 / 27 (22.22%) 7
Abdominal pain upper subjects affected / exposed occurrences (all)	16 / 178 (8.99%) 17	12 / 180 (6.67%) 15	2 / 27 (7.41%) 2
Constipation subjects affected / exposed occurrences (all)	31 / 178 (17.42%) 37	25 / 180 (13.89%) 26	3 / 27 (11.11%) 3
Diarrhoea subjects affected / exposed occurrences (all)	73 / 178 (41.01%) 117	66 / 180 (36.67%) 125	11 / 27 (40.74%) 16
Dry mouth subjects affected / exposed occurrences (all)	28 / 178 (15.73%) 30	16 / 180 (8.89%) 17	3 / 27 (11.11%) 4
Nausea subjects affected / exposed occurrences (all)	49 / 178 (27.53%) 77	41 / 180 (22.78%) 59	9 / 27 (33.33%) 10
Vomiting subjects affected / exposed occurrences (all)	34 / 178 (19.10%) 49	28 / 180 (15.56%) 40	4 / 27 (14.81%) 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 occurrences (all)	4 / 178 (2.25%) 4	1 / 180 (0.56%) 1	2 / 27 (7.41%) 2
Hepatic cytolysis			
subjects affected / exposed occurrences (all)	6 / 178 (3.37%) 6	6 / 180 (3.33%) 6	3 / 27 (11.11%) 3
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed occurrences (all)	11 / 178 (6.18%) 11	8 / 180 (4.44%) 8	0 / 27 (0.00%) 0
Eczema			
subjects affected / exposed occurrences (all)	3 / 178 (1.69%) 3	4 / 180 (2.22%) 4	4 / 27 (14.81%) 5
Intertrigo			
subjects affected / exposed occurrences (all)	1 / 178 (0.56%) 1	3 / 180 (1.67%) 3	2 / 27 (7.41%) 2
Night sweats			
subjects affected / exposed occurrences (all)	6 / 178 (3.37%) 7	4 / 180 (2.22%) 5	2 / 27 (7.41%) 2
Pruritus			
subjects affected / exposed occurrences (all)	60 / 178 (33.71%) 79	55 / 180 (30.56%) 69	13 / 27 (48.15%) 18
Rash			
subjects affected / exposed occurrences (all)	54 / 178 (30.34%) 69	42 / 180 (23.33%) 51	0 / 27 (0.00%) 0
Rash macular			
subjects affected / exposed occurrences (all)	8 / 178 (4.49%) 8	7 / 180 (3.89%) 7	2 / 27 (7.41%) 2
Rash maculo-papular			
subjects affected / exposed occurrences (all)	17 / 178 (9.55%) 18	10 / 180 (5.56%) 13	5 / 27 (18.52%) 5
Skin hypopigmentation			

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported