Clinical trial results:
A Phase 3, Randomized, Double-Blind Study of BMS-936558 (Nivolumab) vs Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Summary

EudraCT number	2012-003718-16
Trial protocol	DE FI SE ES DK NO IT PL GR
Global end of trial date	14 May 2021

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information

Trial identification

Sponsor protocol code	CA209-066

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721772
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the clinical benefit, as measured by the duration of OS, provided by BMS-936558 (Nivolumab) vs. dacarbazine in subjects with previously untreated, 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	18 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Finland: 9
Country: Number of subjects enrolled	France: 66
Country: Number of subjects enrolled	Germany: 51
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	Sweden: 14
Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 71
Country: Number of subjects enrolled	Chile: 8
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Poland: 25
Worldwide total number of subjects	418
EEA total number of subjects	290

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	199
From 65 to 84 years	214
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

418 were randomized (210 to nivolumab, 208 to dacarbazine) and 411 received treatment (206 with nivolumab, 205 with dacarbazine).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine

Arm description:

Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

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:

3 mg/kg solution administered intravenously (IV)

Arm title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab

Arm description:

Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

Arm type	Experimental
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m^2 solution administered intravenously (IV)

Number of subjects in period 1	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Started	210	208
Completed	206	205
Not completed	4	3
Participant withdrew consent	-	1
Participant no longer meets study criteria	3	1
Adverse event unrelated to study drug	1	-
Poor/non-compliance	-	1

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine

Arm description:

Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

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:

3 mg/kg solution administered intravenously (IV)

Arm title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab

Arm description:

Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

Arm type	Active comparator
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m^2 solution administered intravenously (IV)

Number of subjects in period 2	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Started	206	205
Completed	0	0
Not completed	206	205
Adverse event, serious fatal	1	-
Disease progression	119	168
Participant withdrew consent	2	5
Study drug toxicity	19	10
Not reported	1	-
Maximum clinical benefit	16	4
Not specified	19	2
Adverse event unrelated to study drug	7	7
Lost to follow-up	-	1
Poor/non-compliance	1	-
Participant request to discontinue study treatment	21	8

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine
Reporting group description:	
Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	
Reporting group title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Reporting group description:	
Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	

Reporting group values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab	Total
Number of subjects	210	208	418
Age Categorical Units:			
Younger than 65 years	105	94	199
65 to younger than 75 years	78	74	152
75 years and older	27	40	67
Age Continuous Units: Years			
arithmetic mean	61.6	63.7	
standard deviation	± 13.00	± 12.60	-
Sex: Female, Male Units:			
Female	89	83	172
Male	121	125	246
Race/Ethnicity, Customized Units: Subjects			
White	209	207	416
Black or African American	0	0	0
Asian	0	1	1
American Indian or Alaskan native	0	0	0
Other	1	0	1

End points

End points reporting groups

Reporting group title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine
Reporting group description:	
Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	
Reporting group title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Reporting group description:	
Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	
Reporting group title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine
Reporting group description:	
Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	
Reporting group title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Reporting group description:	
Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS is defined as the time between the date of randomization and the date of death or the last date the participant was known to be alive. "999"=N/A	
End point type	Primary
End point timeframe:	
From date of randomization to date of death. For those without documentation of death, to the last date the participant was known to be alive, assessed up to 17 months.	

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210[1]	208		
Units: Months				
median (confidence interval 95%)	999 (999 to 999)	10.84 (9.33 to 12.09)		

Notes:

[1] - Median, upper and lower limit survival were not reached due to insufficient number of events.

Statistical analyses

Statistical analysis title	Overall Survival Hazard Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.6

Primary: Overall survival (OS) Rate

End point title	Overall survival (OS) Rate[2]

End point description:

OS rate is calculated as the percentage of participants alive at the indicated timepoints

End point type	Primary

End point timeframe:

From randomization to 6 months and 12 months

Notes:

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

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Percentage of participants				
number (confidence interval 95%)				
At 6 months	84.1 (78.3 to 88.5)	71.8 (64.9 to 77.6)		
At 12 months	72.9 (65.5 to 78.9)	42.1 (33.0 to 50.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Investigator-assessed PFS is defined as the time from randomization to the date of the first documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Patients who died without progressing were considered to have progressed on the date of their death. Those who did not progress or die were documented on the date of their last evaluable tumor assessment. Patients who did not have any on-study tumor assessments and did not die were documented on their date of randomization. Those who started any subsequent anticancer therapy without a prior reported progression were documented on the date of their last evaluable tumor assessment prior to initiation of subsequent anticancer therapy.

End point type	Secondary

End point timeframe:

From date of randomization to date of disease progression or death, up to approximately 84 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Months				
median (confidence interval 95%)	5.06 (3.52 to 12.16)	2.17 (2.10 to 2.50)		

Statistical analyses

Statistical analysis title	Progression Free Survival Hazard Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Stratified Log Rank Test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.56

Secondary: Progression-free survival (PFS) Rate

End point title	Progression-free survival (PFS) Rate

End point description:

The PFS rate is the percentage of participants alive at the indicated timepoints

End point type	Secondary

End point timeframe:

From randomization to the specified timepoints, up to 84 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Percentage of participants				
number (confidence interval 95%)				
At 6 months	48.2 (41.0 to 55.0)	20.0 (14.6 to 26.1)		
At 12 months	43.3 (36.3 to 50.2)	7.4 (3.9 to 12.4)		
At 18 months	40.5 (33.5 to 47.4)	5.2 (2.2 to 10.2)		
At 24 months	35.8 (29.0 to 42.6)	5.2 (2.2 to 10.2)		
At 36 months	32.8 (26.1 to 39.6)	3.9 (1.3 to 8.9)		
At 48 months	29.7 (23.2 to 36.5)	3.9 (1.3 to 8.9)		
At 60 months	28.4 (22.0 to 35.2)	3.9 (1.3 to 8.9)		
At 72 months	27.8 (21.4 to 34.5)	3.9 (1.3 to 8.9)		
At 84 months	25.9 (19.5 to 32.7)	3.9 (1.3 to 8.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

ORR is defined as the percentage of participants with a best overall response of Response Evaluation Criteria in Solid Tumors (RECIST) defined complete response (CR) or partial response (PR). RECIST, volume 1.1 for target lesions: CR=disappearance of all target lesions; PR=at least a 30% decrease in the sum of the longest dimension (LD) of target lesions, taking as reference the baseline sum LD; stable disease=neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum LD since the treatment started; PD=at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions, and the sum LD must have an absolute increase of ≥5 mm.

End point type	Secondary

End point timeframe:

Tumor assessments beginning at 9 weeks following randomization and continuing every 6 weeks for the first year, then every 12 weeks thereafter until disease progression or death, assessed up to 94 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Percentage of participants				
number (confidence interval 95%)	42.4 (35.6 to 49.4)	14.4 (9.9 to 19.9)		

Statistical analyses

Statistical analysis title	Objective Response Rate Odds Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	4.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.75
upper limit	7.13

Secondary: Overall Survival by Programmed cell death ligand 1 (PD-L1) Expression Level

End point title	Overall Survival by Programmed cell death ligand 1 (PD-L1) Expression Level

End point description:

Overall Survival is defined as the time between the date of randomization and the date of death or the last date the participant was known to be alive. PD-L1 expression level is defined as the percent of tumor cells demonstrating plasma membrane PD-L1-staining in a minimum of 100 evaluable tumor cells per a Dako PD-L1 IHC (immunohistochemistry) assay (referred to as quantifiable PD-L1 expression). Assessment of OS by PD-L1 expression as measured by a validated assay and comparing OS in patients with tumor PD-L1 expression ≥5% (PD-L1 positive) versus patients with tumor PD-L1 expression <5% (PD-L1 negative). Tumor tissue samples for PD-L1 testing were collected at screening from metastatic or unresectable sites prior to randomization.

"999"=N/A

End point type	Secondary

End point timeframe:

From date of randomization to date of disease progression or death, up to approximately 94 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Months				
median (confidence interval 95%)				
PD-L1 positive participants	53.36 (31.47 to 999)	12.39 (9.33 to 18.99)		
PD-L1 negative/indeterminate participants	26.97 (16.36 to 39.79)	10.84 (8.38 to 12.25)		

Statistical analyses

Statistical analysis title	Overall Survival by PD-L1 Hazard Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Unstratified Hazard Ratio
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.24
upper limit	0.56

Statistical analysis title	Overall Survival by PD-L1 Hazard Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Unstratified Hazard Ratio
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.8

Secondary: Change from Baseline in Health-related Quality of Life (HRQoL) Scores

End point title	Change from Baseline in Health-related Quality of Life (HRQoL) Scores

End point description:

HRQoL is evaluated by mean changes from baseline in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status/quality of life composite scale in all randomized patients. The QLQ-30 is a cancer-specific, self-administered questionnaire that contains 30 questions, covering global, functional, and symptom scales. Scores range from 0 to 100. Higher scores on global and functional scales indicate better quality of life (QoL), while higher scores on the symptom scales indicate declining QoL.

"999"=N/A

End point type	Secondary

End point timeframe:

At baseline and every 6 weeks for 12 months and at follow-up visits 1 and 2, assessed up to 93 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Units on a scale				
arithmetic mean (standard deviation)				
Week 7	1.39 (± 19.46)	2.32 (± 20.52)		
Week 13	1.49 (± 18.91)	3.81 (± 16.33)		
Week 19	3.07 (± 16.58)	3.15 (± 17.16)		
Week 25	3.52 (± 20.25)	-0.76 (± 21.28)		
Week 31	2.53 (± 20.46)	4.17 (± 17.83)		
Week 37	3.26 (± 17.61)	7.14 (± 18.45)		
Week 43	1.69 (± 20.24)	-1.04 (± 18.06)		
Week 49	4.31 (± 18.95)	3.33 (± 13.94)		
Week 55	2.92 (± 18.26)	12.50 (± 23.42)		
Week 61	1.79 (± 18.72)	13.89 (± 17.35)		
Week 67	2.08 (± 21.92)	8.33 (± 11.79)		
Week 73	4.69 (± 17.10)	12.50 (± 5.89)		
Week 79	5.62 (± 18.84)	8.33 (± 11.79)		
Week 85	3.05 (± 19.43)	12.50 (± 5.89)		
Week 91	3.66 (± 20.92)	16.67 (± 0.00)		
Week 97	4.27 (± 19.48)	8.33 (± 11.79)		
Week 103	6.20 (± 19.56)	0.00 (± 0.00)		
Week 109	3.83 (± 20.75)	8.33 (± 11.79)		
Week 115	4.17 (± 21.15)	0.00 (± 0.00)		
Week 121	1.47 (± 20.25)	0.00 (± 0.00)		

Week 127	-0.26 (± 19.91)	999 (± 999)		
Week 133	3.16 (± 22.09)	16.67 (± 999)		
Week 139	1.11 (± 21.86)	16.67 (± 999)		
Week 145	4.69 (± 20.07)	16.67 (± 999)		
Week 151	1.67 (± 20.34)	16.67 (± 999)		
Week 157	3.53 (± 22.99)	33.33 (± 999)		
Week 163	7.94 (± 20.83)	16.67 (± 999)		
Week 169	13.33 (± 17.61)	33.33 (± 999)		
Week 175	7.84 (± 23.66)	50.00 (± 999)		
Week 181	5.42 (± 21.16)	999 (± 999)		
Week 187	1.85 (± 22.06)	33.33 (± 999)		
Week 193	2.50 (± 20.96)	16.67 (± 999)		
Week 199	6.77 (± 21.13)	33.33 (± 999)		
Week 205	0.93 (± 24.07)	33.33 (± 999)		
Week 211	0.49 (± 18.97)	999 (± 999)		
Week 217	1.19 (± 23.32)	33.33 (± 999)		
Week 223	5.26 (± 25.49)	33.33 (± 999)		
Week 229	5.56 (± 23.77)	16.67 (± 999)		
Week 235	5.39 (± 24.82)	999 (± 999)		
Week 241	2.78 (± 25.72)	999 (± 999)		
Week 247	5.36 (± 25.45)	16.67 (± 999)		
Week 253	3.89 (± 26.89)	16.67 (± 999)		
Week 259	7.05 (± 24.26)	25.00 (± 999)		
Week 265	8.93 (± 21.55)	33.33 (± 999)		
Week 271	6.25 (± 21.94)	999 (± 999)		
Week 277	4.17 (± 21.12)	25.00 (± 999)		
Week 283	5.56 (± 21.42)	33.33 (± 999)		
Week 289	3.57 (± 20.86)	33.33 (± 999)		
Week 295	3.47 (± 23.15)	16.67 (± 999)		
Week 301	2.78 (± 23.92)	16.67 (± 999)		
Week 307	1.52 (± 24.95)	33.33 (± 999)		
Week 313	9.17 (± 24.04)	999 (± 999)		
Week 319	3.33 (± 26.70)	33.33 (± 999)		
Week 325	9.38 (± 25.37)	999 (± 999)		
Week 331	10.71 (± 27.09)	33.33 (± 999)		
Week 337	11.90 (± 26.29)	999 (± 999)		
Week 343	16.67 (± 26.35)	999 (± 999)		
Week 349	9.52 (± 26.54)	999 (± 999)		
Week 355	0 (± 10.21)	999 (± 999)		
Week 361	20.83 (± 30.81)	999 (± 999)		
Week 367	25.00 (± 36.32)	999 (± 999)		
Week 373	25.00 (± 36.32)	999 (± 999)		
Week 379	8.33 (± 999)	999 (± 999)		
Week 385	8.33 (± 999)	999 (± 999)		
Week 391	8.33 (± 999)	999 (± 999)		
Week 397	8.33 (± 999)	999 (± 999)		

Week 403	8.33 (± 999)	999 (± 999)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival (OS) Extended

End point title	Overall Survival (OS) Extended

End point description:

OS is defined as the time between the date of randomization and the date of death. For those without documentation of death, OS will be censored on the last date the participant was known to be alive. OS data for this endpoint was collected past the primary completion date up until study completion.

End point type	Post-hoc

End point timeframe:

From date of randomization to date of death. For those without documentation of death, to the last date the participant was known to be alive, assessed up to 94 months.

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Months				
median (confidence interval 95%)	37.29 (25.40 to 51.55)	11.17 (9.56 to 12.98)		

Statistical analyses

Statistical analysis title	Overall Survival Extended Hazard Ratio
Comparison groups	Nivolumab, 3 mg/kg + placebo-matching dacarbazine v Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab
Number of subjects included in analysis	418
Analysis specification	Post-hoc
Analysis type	
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.65

Post-hoc: Overall Survival (OS) Rate Extended

End point title	Overall Survival (OS) Rate Extended

End point description:

OS rate is calculated as the percentage of participants alive at the indicated timepoints. Data for this endpoint was collected after the primary completion date up until study completion. The OS rate for the 6 month and 12 month timepoints reflect updated data that was collected after the primary completion date.

End point type	Post-hoc

End point timeframe:

From randomization to the specified timepoints, up to 84 months

End point values	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	210	208		
Units: Percentage of participants				
median (confidence interval 95%)				
6 months	48.2 (41.0 to 55.0)	20.0 (14.6 to 26.1)		
12 months	43.3 (36.3 to 50.2)	7.4 (3.9 to 12.4)		
18 months	63.8 (56.8 to 70.0)	36.7 (30.0 to 43.3)		
24 months	57.8 (50.7 to 64.2)	26.3 (20.4 to 32.6)		
36 months	50.8 (43.7 to 57.5)	21.6 (16.1 to 27.6)		
48 months	43.8 (36.9 to 50.5)	17.9 (12.9 to 23.6)		
60 months	39.3 (32.6 to 46.0)	17.4 (12.4 to 23.0)		
72 months	37.3 (30.7 to 43.9)	16.9 (12.0 to 22.5)		
84 months	36.2 (29.5 to 42.8)	16.9 (12.0 to 22.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose to 100 days following date of last dose (up to approximately 97 months).

Adverse event reporting additional description:

All randomized subjects

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab

Reporting group description:

Participants received dacarbazine 1000 mg/m^2, solution administered IV every 3 weeks with placebo-matching nivolumab solution administered IV every 2 weeks until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

Reporting group title	Nivolumab, 3 mg/kg + placebo-matching dacarbazine

Reporting group description:

Participants received nivolumab, 3 mg/kg, solution administered Intravenously (IV) every 2 weeks with placebo-matching dacarbazine solution administered IV every 3 weeks, until disease progression, discontinuation due to toxicity, withdrawal of consent, or study completion

Serious adverse events	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	
Total subjects affected by serious adverse events			
subjects affected / exposed	119 / 205 (58.05%)	125 / 206 (60.68%)	
number of deaths (all causes)	165	126	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 205 (0.00%)	8 / 206 (3.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen's disease			

subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal adenocarcinoma			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 205 (0.49%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	69 / 205 (33.66%)	32 / 206 (15.53%)	
occurrences causally related to treatment / all	0 / 72	0 / 35	
deaths causally related to treatment / all	0 / 61	0 / 26	
Melanoma recurrent			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 205 (0.49%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	3 / 205 (1.46%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Neoplasm			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodular melanoma			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin neoplasm bleeding			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			

subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Ectopic pregnancy			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chills			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 205 (1.46%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 205 (2.93%)	6 / 206 (2.91%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 3	0 / 2	

Injection site reaction			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site reaction			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	6 / 205 (2.93%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	2 / 205 (0.98%)	4 / 206 (1.94%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Endometriosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 205 (0.00%)	4 / 206 (1.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	7 / 205 (3.41%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 205 (3.41%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	2 / 205 (0.98%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 205 (1.95%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mania			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood calcium decreased			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical condition abnormal			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Oxygen saturation decreased			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic enzymes abnormal			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lumbar vertebral fracture			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation skin injury			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neurological decompensation			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Presyncope			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 205 (0.98%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression			

subjects affected / exposed	2 / 205 (0.98%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Transient ischaemic attack			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 205 (0.98%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 205 (1.95%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 205 (1.95%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Deafness unilateral			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid retraction			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	2 / 205 (0.98%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	4 / 205 (1.95%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 205 (0.49%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 205 (0.49%)	4 / 206 (1.94%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	4 / 205 (1.95%)	6 / 206 (2.91%)	
occurrences causally related to treatment / all	1 / 4	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	2 / 205 (0.98%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric mucosal lesion			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	2 / 205 (0.98%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 205 (0.00%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash papular			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoid-like reaction			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin lesion			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	3 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Haematuria			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypophysitis			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 205 (0.98%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Infections and infestations			
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 205 (0.98%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Erysipelas			
subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 205 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 205 (0.49%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 205 (0.98%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 205 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 205 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 205 (0.49%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 205 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dacarbazine, 1000 mg/m^2 + placebo-matching nivolumab	Nivolumab, 3 mg/kg + placebo-matching dacarbazine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	187 / 205 (91.22%)	191 / 206 (92.72%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 205 (2.44%)	22 / 206 (10.68%)	
occurrences (all)	5	26	
Hypotension			
subjects affected / exposed	11 / 205 (5.37%)	5 / 206 (2.43%)	
occurrences (all)	11	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	38 / 205 (18.54%)	43 / 206 (20.87%)	
occurrences (all)	60	86	
Influenza like illness			
subjects affected / exposed	4 / 205 (1.95%)	13 / 206 (6.31%)	
occurrences (all)	4	16	
Fatigue			
subjects affected / exposed	60 / 205 (29.27%)	77 / 206 (37.38%)	
occurrences (all)	77	113	
Oedema peripheral			
subjects affected / exposed	11 / 205 (5.37%)	26 / 206 (12.62%)	
occurrences (all)	12	31	
Pyrexia			
subjects affected / exposed	29 / 205 (14.15%)	36 / 206 (17.48%)	
occurrences (all)	37	65	
Pain			

subjects affected / exposed	13 / 205 (6.34%)	13 / 206 (6.31%)	
occurrences (all)	13	16	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 205 (14.15%)	40 / 206 (19.42%)	
occurrences (all)	32	59	
Dyspnoea			
subjects affected / exposed	25 / 205 (12.20%)	25 / 206 (12.14%)	
occurrences (all)	28	27	
Oropharyngeal pain			
subjects affected / exposed	4 / 205 (1.95%)	11 / 206 (5.34%)	
occurrences (all)	6	12	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 205 (5.85%)	16 / 206 (7.77%)	
occurrences (all)	12	17	
Insomnia			
subjects affected / exposed	9 / 205 (4.39%)	15 / 206 (7.28%)	
occurrences (all)	9	16	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 205 (3.41%)	17 / 206 (8.25%)	
occurrences (all)	8	21	
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 205 (3.90%)	12 / 206 (5.83%)	
occurrences (all)	8	17	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 205 (3.41%)	12 / 206 (5.83%)	
occurrences (all)	7	14	
Blood creatinine increased			
subjects affected / exposed	6 / 205 (2.93%)	12 / 206 (5.83%)	
occurrences (all)	6	15	
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 205 (2.93%)	13 / 206 (6.31%)	
occurrences (all)	6	13	

Platelet count decreased			
subjects affected / exposed	11 / 205 (5.37%)	0 / 206 (0.00%)	
occurrences (all)	16	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 205 (7.32%)	14 / 206 (6.80%)	
occurrences (all)	20	21	
Headache			
subjects affected / exposed	32 / 205 (15.61%)	45 / 206 (21.84%)	
occurrences (all)	52	72	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	26 / 205 (12.68%)	1 / 206 (0.49%)	
occurrences (all)	48	2	
Anaemia			
subjects affected / exposed	24 / 205 (11.71%)	26 / 206 (12.62%)	
occurrences (all)	34	39	
Thrombocytopenia			
subjects affected / exposed	22 / 205 (10.73%)	2 / 206 (0.97%)	
occurrences (all)	48	2	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 205 (10.24%)	30 / 206 (14.56%)	
occurrences (all)	26	35	
Abdominal pain upper			
subjects affected / exposed	12 / 205 (5.85%)	17 / 206 (8.25%)	
occurrences (all)	12	21	
Constipation			
subjects affected / exposed	57 / 205 (27.80%)	57 / 206 (27.67%)	
occurrences (all)	81	89	
Diarrhoea			
subjects affected / exposed	58 / 205 (28.29%)	75 / 206 (36.41%)	
occurrences (all)	94	159	
Dyspepsia			
subjects affected / exposed	7 / 205 (3.41%)	11 / 206 (5.34%)	
occurrences (all)	7	15	
Nausea			

subjects affected / exposed	104 / 205 (50.73%)	59 / 206 (28.64%)	
occurrences (all)	180	95	
Vomiting			
subjects affected / exposed	54 / 205 (26.34%)	34 / 206 (16.50%)	
occurrences (all)	72	53	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 205 (0.49%)	14 / 206 (6.80%)	
occurrences (all)	1	17	
Dry skin			
subjects affected / exposed	5 / 205 (2.44%)	21 / 206 (10.19%)	
occurrences (all)	5	24	
Erythema			
subjects affected / exposed	7 / 205 (3.41%)	29 / 206 (14.08%)	
occurrences (all)	7	41	
Pruritus			
subjects affected / exposed	40 / 205 (19.51%)	64 / 206 (31.07%)	
occurrences (all)	45	100	
Photosensitivity reaction			
subjects affected / exposed	12 / 205 (5.85%)	5 / 206 (2.43%)	
occurrences (all)	13	5	
Rash			
subjects affected / exposed	29 / 205 (14.15%)	63 / 206 (30.58%)	
occurrences (all)	32	99	
Vitiligo			
subjects affected / exposed	3 / 205 (1.46%)	37 / 206 (17.96%)	
occurrences (all)	3	38	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	3 / 205 (1.46%)	11 / 206 (5.34%)	
occurrences (all)	3	11	
Hypothyroidism			
subjects affected / exposed	8 / 205 (3.90%)	20 / 206 (9.71%)	
occurrences (all)	9	21	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	29 / 205 (14.15%)	46 / 206 (22.33%)	
occurrences (all)	35	69	
Back pain			
subjects affected / exposed	23 / 205 (11.22%)	39 / 206 (18.93%)	
occurrences (all)	26	51	
Myalgia			
subjects affected / exposed	13 / 205 (6.34%)	18 / 206 (8.74%)	
occurrences (all)	17	28	
Pain in extremity			
subjects affected / exposed	20 / 205 (9.76%)	34 / 206 (16.50%)	
occurrences (all)	22	52	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 205 (1.95%)	12 / 206 (5.83%)	
occurrences (all)	4	15	
Influenza			
subjects affected / exposed	3 / 205 (1.46%)	15 / 206 (7.28%)	
occurrences (all)	4	22	
Nasopharyngitis			
subjects affected / exposed	10 / 205 (4.88%)	34 / 206 (16.50%)	
occurrences (all)	13	67	
Rhinitis			
subjects affected / exposed	3 / 205 (1.46%)	12 / 206 (5.83%)	
occurrences (all)	3	14	
Upper respiratory tract infection			
subjects affected / exposed	13 / 205 (6.34%)	20 / 206 (9.71%)	
occurrences (all)	13	28	
Urinary tract infection			
subjects affected / exposed	11 / 205 (5.37%)	13 / 206 (6.31%)	
occurrences (all)	11	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 205 (18.05%)	40 / 206 (19.42%)	
occurrences (all)	40	51	
Hyperglycaemia			

subjects affected / exposed occurrences (all)	0 / 205 (0.00%) 0	14 / 206 (6.80%) 16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2013	Inclusion of non-clinical safety findings related to reproductive toxicology data.
08 May 2013	Removes the specified timeframe around the timing of tumor tissue collection for inclusion. Inclusion of recommendations for adverse events management in subjects requiring treatment with high dose steroids or other immunosuppressive agents. Expanded allowance for palliative therapy at time of treatment beyond progression.
09 July 2014	This amendment provides modifications to the protocol based on recommendations of the study's Data Monitoring Committee (DMC).
06 May 2015	Update to follow-up data collection of the overall survival endpoint and the definition of the protocol defined window.
23 September 2016	Update to nivolumab dosing and schedule, added contraception requirements, change in tumor assessment frequency for the dacarbazine arm, EQ-5D assessment frequency changed, Immunogenicity/PK assessment requirement removed, Efficacy Assessments changed, and Pharmacokinetic/Immunogenicity Assessments changed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

An independent data monitoring committee (DMC) found that data from a DMC-requested database lock showed clear survival benefit with nivolumab and thus recommended unblinding the study and switching patients randomized to dacarbazine to nivolumab.

Notes: