Clinical trial results:
A DOSE FREQUENCY OPTIMIZATION, PHASE IIIB/IV TRIAL OF NIVOLUMAB 240 MG EVERY 2 WEEKS VS NIVOLUMAB 480 MG EVERY 4 WEEKS IN SUBJECTS WITH ADVANCED OR METASTATIC NON-SMALL CELL LUNG CANCER WHO RECEIVED UP TO 12 MONTHS OF NIVOLUMAB AT 3 MG/KG OR 240 MG EVERY 2 WEEKS

Summary

EudraCT number	2015-004633-27
Trial protocol	DE IE AT ES IT FR
Global end of trial date	18 February 2022

Results information

Result version number	v1 (current)
This version publication date	03 February 2023
First version publication date	03 February 2023

Trial information

Trial identification

Sponsor protocol code	CA209-384

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02713867
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	22 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The coprimary objectives are to compare the PFS rate at 6 months after randomization and PFS rate at 1 year after randomization, as measured by investigator-assessed response using Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, of nivolumab 3 mg/kg every 2 weeks (Arm 1) and nivolumab 6 mg/kg every 4 weeks (Arm 2) in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq).

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 subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 April 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 21
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 108
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	363
EEA total number of subjects	208

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)	143
From 65 to 84 years	213
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:
363 Randomized, 358 Treated

Period 1

Period 1 title	Randomization
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab 480mg

Arm description:
Nivolumab 480mg Q4W

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:
480mg Q4W

Arm title	Nivolumab 240mg

Arm description:
Nivolumab 240mg Q2W

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:
240mg Q2W

Number of subjects in period 1	Nivolumab 480mg	Nivolumab 240mg
Started	180	183
Completed	178	180
Not completed	2	3
Other Reason	2	1
Participant Withdrew consent	-	2

Period 2	
Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Nivolumab 480mg

Arm description:
Nivolumab 480mg Q4W

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:
480mg Q4W

Arm title	Nivolumab 240mg

Arm description:
Nivolumab 240mg Q2W

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:
240mg Q2W

Number of subjects in period 2	Nivolumab 480mg	Nivolumab 240mg
Started	178	180
Completed	0	0
Not completed	178	180
Adverse event, serious fatal	7	3
Requested to Discontinue	8	8
Other Reasons	22	28
Poor/Non Compliance	1	-
Maximum Clinical Benefit	5	6
No longer meets study criteria	2	1

Study Drug Toxicity	16	19
Withdrew consent	3	6
AE unrelated to Study Drug	11	10
Disease Progression	82	83
Administrative reason by sponsor	21	16

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab 480mg
Reporting group description: Nivolumab 480mg Q4W	
Reporting group title	Nivolumab 240mg
Reporting group description: Nivolumab 240mg Q2W	

Reporting group values	Nivolumab 480mg	Nivolumab 240mg	Total
Number of subjects	180	183	363
Age categorical Units: Subjects			
Adults (18-64 years)	75	68	143
From 65-84 years	100	113	213
85 years and over	5	2	7
Age Continuous Units: Years			
arithmetic mean	66.4	66.5	
standard deviation	± 9.25	± 8.65	-
Sex: Female, Male Units: Participants			
Female	49	54	103
Male	131	129	260
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	3	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	8	16
White	169	167	336
More than one race	0	0	0
Unknown or Not Reported	2	5	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	4	7
Not Hispanic or Latino	118	115	233
Unknown or Not Reported	59	64	123

End points

End points reporting groups

Reporting group title	Nivolumab 480mg
Reporting group description: Nivolumab 480mg Q4W	
Reporting group title	Nivolumab 240mg
Reporting group description: Nivolumab 240mg Q2W	
Reporting group title	Nivolumab 480mg
Reporting group description: Nivolumab 480mg Q4W	
Reporting group title	Nivolumab 240mg
Reporting group description: Nivolumab 240mg Q2W	

Primary: Progression Free Survival Rate (PFSR) at 12 Months

End point title	Progression Free Survival Rate (PFSR) at 12 Months[1]

End point description:

The proportion of participants remaining progression free and surviving at 6 months. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

End point type	Primary

End point timeframe:

At 12 Months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No Statistical Analysis done for this endpoint

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of Participants				
number (confidence interval 95%)	0.53 (0.46 to 0.61)	0.55 (0.47 to 0.62)		

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival Rate (PFSR) at 6 Months

End point title	Progression Free Survival Rate (PFSR) at 6 Months[2]

End point description:

The proportion of participants remaining progression free and surviving at 6 months. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

End point type	Primary

End point timeframe:

At 6 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: No Statistical Analysis done for this endpoint

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of Participants				
number (confidence interval 95%)	0.76 (0.70 to 0.83)	0.79 (0.73 to 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Adverse Events (AEs)

End point title	Percentage of Participants with an Adverse Events (AEs)

End point description:

Percentage of participants with an Adverse Event due to any cause

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)	91.6	97.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Serious Adverse Events (SAEs)

End point title	Percentage of Participants with an Serious Adverse Events (SAEs)

End point description:

Percentage of participants with an Serious Adverse Event due to any cause.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:
1)results in death
2) is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
3) requires inpatient hospitalization or causes prolongation of existing hospitalization
4) results in persistent or significant disability/incapacity
5) is a congenital anomaly/birth defect
6) is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.)

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)	34.8	39.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Adverse Events Leading to Discontinuation (AEsDC)

End point title	Percentage of Participants with an Adverse Events Leading to Discontinuation (AEsDC)

End point description:

Percentage of Participants with an Adverse Event leading to discontinuation (AEsDC) due to any cause.

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)	19.1	17.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Immune Mediated Adverse Events (IMAEs)

End point title	Percentage of Participants with an Immune Mediated Adverse Events (IMAEs)

End point description:

Percentage of Participants with an Immune Mediated Adverse Events treated with Immune-Modulating Medication

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)				
Diarrhea/Colitis	3.4	5.0		
Hepatitis	0.0	1.7		
Pneumonitis	3.4	3.3		
Nephritis and Renal Dysfunction	0.6	0.0		
Rash	7.3	7.2		
Hypersensitivity/Infusion Reaction	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Select Adverse Events

End point title	Percentage of Participants with an Select Adverse Events

End point description:

Percentage of Participants with an Select Adverse Event due to any cause

Select adverse events include adverse events in the following systems: Gastrointestinal, Hepatic, Pulmonary, Renal, Skin, Hypersensitivity/Infusion reaction and Endrocrine.

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)				
Gastrointestinal	18.5	25.0		
Hepatic	2.2	10.0		
Pulmonary	6.7	5.0		
Renal	10.1	5.6		
Skin	30.9	33.9		
Hypersensitivity/Infusion Reaction	0.0	1.1		
Endocrine	16.3	18.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Event of Special Interest (ESI)

End point title	Percentage of Participants with an Event of Special Interest (ESI)

End point description:

Other ESI included the following categories: demyelination, encephalitis, Guillain-Barré syndrome (GBS), myasthenic syndrome, pancreatitis, uveitis, myositis, myocarditis, rhabdomyolysis, and Graft Versus Host Disease (GVHD).

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)				
Pancreatitis	1.1	2.8		
demyelination	0	0		
encephalitis	0	0		
GBS	0	0		
myasthenic syndrome	0	0		
uveitis	0	0		

myositis	0	0		
myocarditis	0	0		
rhabdomyolysis	0	0		
GVHD	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Test Abnormalities

End point title	Number of Participants with Laboratory Test Abnormalities

End point description:

Number of participants with any laboratory test result that is clinically significant or meets the definition of an SAE (Grade 3+4 combined)

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Number of Participants				
Alanine Aminotransferase	1	1		
Alkaline Phosphate	1	0		
Aspartate Aminotransferase	1	2		
Bilirubin, Total	1	1		
Creatinine	1	2		
Hemoglobin	0	4		
Hypercalcemia	2	5		
Hyperkalemia	4	3		
Hypermagnesemia	4	5		
Hypernatremia	0	0		
Hypocalcemia	4	6		
Hypokalemia	3	6		
Hypomagnesemia	3	2		
Hypnatremia	6	7		
Leukocytes	1	3		
Lymphocytes	22	21		
Neutrophils	3	4		
Platelet Count	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFSR) at 24 Months

End point title	Progression Free Survival Rate (PFSR) at 24 Months

End point description:

The proportion of participants remaining progression free and surviving at 6 months. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

At 24 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of Participants				
number (confidence interval 95%)	0.34 (0.27 to 0.42)	0.35 (0.28 to 0.43)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFSR) by Tumor Histology at 12 Months

End point title	Progression Free Survival Rate (PFSR) by Tumor Histology at 12 Months

End point description:

The proportion of participants remaining progression free and surviving at 6 months. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

End point type	Secondary

End point timeframe:

At 12 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of Participants				
number (confidence interval 95%)				
Squamous	0.50 (0.37 to 0.64)	0.42 (0.29 to 0.55)		
Non Squamous	0.54 (0.45 to 0.63)	0.60 (0.51 to 0.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Rate (PFSR) by Response Criteria at 12 Months

End point title	Progression Free Survival Rate (PFSR) by Response Criteria at 12 Months

End point description:

The proportion of participants remaining progression free and surviving at 12 months. Participants who did not progress or die will be censored on the date of their last evaluable tumor assessment. Progression is defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

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.
Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

End point type	Secondary

End point timeframe:

At 12 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of Participants				
number (confidence interval 95%)				
Complete Remission (CR)/Partial Remission (PR)	0.63 (0.51 to 0.75)	0.66 (0.53 to 0.78)		
Stable Disease (SD)	0.47 (0.38 to 0.57)	0.48 (0.39 to 0.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate at 12 Months

End point title	Overall Survival (OS) Rate at 12 Months

End point description:

The proportion of participants alive at 12 months. OS is defined as time from the date of randomization to the date of death. Participants who did not die by the end of the study will be censored at the last known date alive.

End point type	Secondary

End point timeframe:

At 12 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	142	150		
Units: Proportion of participants				
number (confidence interval 95%)	0.851 (0.799 to 0.902)	0.908 (0.866 to 0.951)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate up to 60 Months

End point title	Overall Survival (OS) Rate up to 60 Months

End point description:

The proportion of participants alive up to 60 months. OS is defined as time from the date of randomization to the date of death. Participants who did not die by the end of the study will be censored at the last known date alive.

Here "99999" means NA

End point type	Secondary

End point timeframe:

From randomization to the date of death, Up to 60 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of participants				
number (confidence interval 95%)				
12 Months	0.82 (0.76 to 0.88)	0.88 (0.83 to 0.93)		
24 Months	0.62 (0.55 to 0.69)	0.70 (0.63 to 0.77)		

36 Months	0.49 (0.42 to 0.57)	0.57 (0.49 to 0.64)		
48 Months	99999 (99999 to 99999)	99999 (99999 to 99999)		
60 Months	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate by Histology at 12 Months

End point title	Overall Survival Rate by Histology at 12 Months

End point description:

The proportion of participants alive at 12 months. OS is defined as time from the date of randomization to the date of death. Participants who did not die by the end of the study will be censored at the last known date alive.

OS rate by histology did not have data collected after 12 months randomization.

End point type	Secondary

End point timeframe:

at 12 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of participants				
number (confidence interval 95%)				
Squamous	0.74 (0.63 to 0.85)	0.80 (0.70 to 0.90)		
Non Squamous	0.86 (0.80 to 0.92)	0.92 (0.87 to 0.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate by Response Criteria at 12 Months

End point title	Overall Survival Rate by Response Criteria at 12 Months

End point description:

The proportion of participants alive at 12 months. OS is defined as time from the date of randomization to the date of death. Participants who did not die by the end of the study will be censored at the last known date alive.

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.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

OS rate by response did not have data collected after 12 months randomization.

End point type	Secondary

End point timeframe:

12 Months

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	180	183		
Units: Proportion of participants				
number (confidence interval 95%)				
CR/PR	0.90 (0.82 to 0.98)	0.93 (0.87 to 1.00)		
SD	0.78 (0.70 to 0.86)	0.85 (0.78 to 0.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who experienced eeath

End point title	Percentage of participants who experienced eeath

End point description:

Percentage of Participants who experienced Death due to any cause

End point type	Secondary

End point timeframe:

Between first dose and 100 days after last dose of study therapy (Approximately Up to 16 months)

End point values	Nivolumab 480mg	Nivolumab 240mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	178	180		
Units: Percentage of Participants				
number (not applicable)	49.4	43.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events and SAEs: between first dose and 100 days after last dose of study therapy (Approximately 16 months up to 56 months).

All Cause Mortality, from randomization to study completion.: Approximately 5 years and 8 months.

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants to study completion.

The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication" or similar.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	NIVOLUMAB 240 mg Q2W
Reporting group description:	
Nivolumab 240mg Q2W	
Reporting group title	NIVOLUMAB 480 mg Q4W
Reporting group description:	
Nivolumab 480mg Q4W	

Serious adverse events	NIVOLUMAB 240 mg Q2W	NIVOLUMAB 480 mg Q4W	
Total subjects affected by serious adverse events			
subjects affected / exposed	78 / 180 (43.33%)	80 / 178 (44.94%)	
number of deaths (all causes)	79	88	
number of deaths resulting from adverse events	15	21	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal cancer			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glottis carcinoma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
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	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	14 / 180 (7.78%)	10 / 178 (5.62%)	
occurrences causally related to treatment / all	0 / 15	0 / 10	
deaths causally related to treatment / all	0 / 8	0 / 8	
Metastases to central nervous system			
subjects affected / exposed	2 / 180 (1.11%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leriche syndrome			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
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			
Asthenia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drowning			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 180 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Acquired phimosis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	2 / 180 (1.11%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	4 / 180 (2.22%)	11 / 178 (6.18%)	
occurrences causally related to treatment / all	0 / 6	0 / 18	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dyspnoea			
subjects affected / exposed	2 / 180 (1.11%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 180 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune-mediated lung disease			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	4 / 180 (2.22%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	3 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 180 (2.22%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femur fracture			
subjects affected / exposed	1 / 180 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal compression fracture			
subjects affected / exposed	2 / 180 (1.11%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 180 (1.11%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery occlusion			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebral ischaemia			

subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nystagmus			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 180 (1.11%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
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	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			

subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 180 (0.56%)	4 / 178 (2.25%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 180 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (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	0 / 180 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subcapsular renal haematoma			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypophysitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
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			
Arthritis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 180 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (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 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoporosis			
subjects affected / exposed	2 / 180 (1.11%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue disorder			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic spinal stenosis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 180 (0.00%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (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	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	3 / 180 (1.67%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			

subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site cellulitis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 180 (5.56%)	8 / 178 (4.49%)	
occurrences causally related to treatment / all	0 / 11	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sepsis			

subjects affected / exposed	3 / 180 (1.67%)	5 / 178 (2.81%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 180 (1.11%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 180 (0.56%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural sepsis			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 180 (0.56%)	2 / 178 (1.12%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperkalaemia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 180 (0.56%)	0 / 178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 180 (0.00%)	1 / 178 (0.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NIVOLUMAB 240 mg Q2W	NIVOLUMAB 480 mg Q4W	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	169 / 180 (93.89%)	146 / 178 (82.02%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 180 (7.22%)	11 / 178 (6.18%)	
occurrences (all)	17	12	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 180 (14.44%)	27 / 178 (15.17%)	
occurrences (all)	34	31	
Fatigue			
subjects affected / exposed	40 / 180 (22.22%)	29 / 178 (16.29%)	
occurrences (all)	48	34	
Non-cardiac chest pain			
subjects affected / exposed	10 / 180 (5.56%)	5 / 178 (2.81%)	
occurrences (all)	11	7	
Pyrexia			
subjects affected / exposed	16 / 180 (8.89%)	17 / 178 (9.55%)	
occurrences (all)	20	20	
Oedema peripheral			
subjects affected / exposed	15 / 180 (8.33%)	14 / 178 (7.87%)	
occurrences (all)	18	14	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	12 / 180 (6.67%)	8 / 178 (4.49%)	
occurrences (all)	13	8	
Cough			
subjects affected / exposed	36 / 180 (20.00%)	25 / 178 (14.04%)	
occurrences (all)	44	31	
Dyspnoea			
subjects affected / exposed	26 / 180 (14.44%)	23 / 178 (12.92%)	
occurrences (all)	28	26	

Pneumonitis			
subjects affected / exposed	7 / 180 (3.89%)	10 / 178 (5.62%)	
occurrences (all)	8	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	21 / 180 (11.67%)	8 / 178 (4.49%)	
occurrences (all)	22	8	
Investigations			
Blood creatinine increased			
subjects affected / exposed	7 / 180 (3.89%)	14 / 178 (7.87%)	
occurrences (all)	10	15	
Lipase increased			
subjects affected / exposed	14 / 180 (7.78%)	8 / 178 (4.49%)	
occurrences (all)	21	11	
Weight decreased			
subjects affected / exposed	20 / 180 (11.11%)	9 / 178 (5.06%)	
occurrences (all)	23	9	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	10 / 180 (5.56%)	10 / 178 (5.62%)	
occurrences (all)	14	12	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 180 (8.89%)	14 / 178 (7.87%)	
occurrences (all)	16	17	
Dizziness			
subjects affected / exposed	17 / 180 (9.44%)	6 / 178 (3.37%)	
occurrences (all)	22	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 180 (11.11%)	12 / 178 (6.74%)	
occurrences (all)	30	15	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 180 (3.89%)	11 / 178 (6.18%)	
occurrences (all)	7	12	
Abdominal pain upper			

subjects affected / exposed	10 / 180 (5.56%)	6 / 178 (3.37%)	
occurrences (all)	11	6	
Constipation			
subjects affected / exposed	24 / 180 (13.33%)	20 / 178 (11.24%)	
occurrences (all)	30	23	
Diarrhoea			
subjects affected / exposed	41 / 180 (22.78%)	31 / 178 (17.42%)	
occurrences (all)	81	41	
Gastrooesophageal reflux disease			
subjects affected / exposed	11 / 180 (6.11%)	7 / 178 (3.93%)	
occurrences (all)	11	8	
Nausea			
subjects affected / exposed	29 / 180 (16.11%)	14 / 178 (7.87%)	
occurrences (all)	36	18	
Vomiting			
subjects affected / exposed	21 / 180 (11.67%)	13 / 178 (7.30%)	
occurrences (all)	27	13	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 180 (6.67%)	6 / 178 (3.37%)	
occurrences (all)	15	6	
Pruritus			
subjects affected / exposed	42 / 180 (23.33%)	32 / 178 (17.98%)	
occurrences (all)	57	38	
Rash maculo-papular			
subjects affected / exposed	6 / 180 (3.33%)	10 / 178 (5.62%)	
occurrences (all)	10	13	
Rash			
subjects affected / exposed	9 / 180 (5.00%)	11 / 178 (6.18%)	
occurrences (all)	10	13	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	17 / 180 (9.44%)	22 / 178 (12.36%)	
occurrences (all)	19	22	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	38 / 180 (21.11%)	24 / 178 (13.48%)	
occurrences (all)	45	25	
Back pain			
subjects affected / exposed	20 / 180 (11.11%)	25 / 178 (14.04%)	
occurrences (all)	24	26	
Muscle spasms			
subjects affected / exposed	11 / 180 (6.11%)	4 / 178 (2.25%)	
occurrences (all)	12	6	
Myalgia			
subjects affected / exposed	11 / 180 (6.11%)	4 / 178 (2.25%)	
occurrences (all)	12	4	
Pain in extremity			
subjects affected / exposed	16 / 180 (8.89%)	13 / 178 (7.30%)	
occurrences (all)	17	14	
Musculoskeletal chest pain			
subjects affected / exposed	5 / 180 (2.78%)	9 / 178 (5.06%)	
occurrences (all)	6	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 180 (8.89%)	11 / 178 (6.18%)	
occurrences (all)	17	20	
Bronchitis			
subjects affected / exposed	23 / 180 (12.78%)	17 / 178 (9.55%)	
occurrences (all)	30	20	
Rhinitis			
subjects affected / exposed	10 / 180 (5.56%)	0 / 178 (0.00%)	
occurrences (all)	12	0	
Pneumonia			
subjects affected / exposed	11 / 180 (6.11%)	9 / 178 (5.06%)	
occurrences (all)	12	9	
Sinusitis			
subjects affected / exposed	11 / 180 (6.11%)	7 / 178 (3.93%)	
occurrences (all)	11	10	
Upper respiratory tract infection			

subjects affected / exposed	16 / 180 (8.89%)	11 / 178 (6.18%)	
occurrences (all)	24	16	
Urinary tract infection			
subjects affected / exposed	12 / 180 (6.67%)	7 / 178 (3.93%)	
occurrences (all)	12	7	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	15 / 180 (8.33%)	4 / 178 (2.25%)	
occurrences (all)	20	4	
Decreased appetite			
subjects affected / exposed	20 / 180 (11.11%)	16 / 178 (8.99%)	
occurrences (all)	22	20	
Hypomagnesaemia			
subjects affected / exposed	10 / 180 (5.56%)	4 / 178 (2.25%)	
occurrences (all)	18	5	
Hypokalaemia			
subjects affected / exposed	10 / 180 (5.56%)	8 / 178 (4.49%)	
occurrences (all)	16	10	
Hypophosphataemia			
subjects affected / exposed	12 / 180 (6.67%)	3 / 178 (1.69%)	
occurrences (all)	17	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 December 2015	Allows enrollment of subjects who are ineligible for or refuse chemotherapy in the first-line advanced non-small cell lung cancer setting Allows use of flat dose in the pre-study period and during the investigational period. Added HIV testing as a screening test
12 February 2016	Change the Human Immunodeficiency Virus criterion to reflect the language that is used across the nivolumab clinical development program and adjusted the frequency of magnetic resonance imaging scans in those with a history of brain metastasis to align with study assessments.
12 August 2016	To change the pre-study nivolumab requirement Add a small increase to the sample size Add immunogenicity as an endpoint Make small changes to the laboratory and tumor assessments and duration of contraception use to align the protocol with updates to the nivolumab clinical development program.
09 February 2018	Included additional language for nivolumab program level updates Added information for interim analysis
18 June 2018	Reduced sample size and modified primary endpoint from noninferiority to one-sided confidence interval around the differences of PFS rates Modified follow-up for overall survival for 3 years Added rationale for maximum treatment duration with nivolumab of 2 years

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.

No formal statistical analyses were conducted. Median OS was not reached in either arm.

Notes: