Clinical trial results:
A Phase III Open-Label, Multicenter Trial of Avelumab (MSB0010718C) Versus Docetaxel in Subjects With Non-Small Cell Lung Cancer That Has Progressed After a Platinum-Containing Doublet

Summary

EudraCT number	2014-005060-15
Trial protocol	SK DE GB BE HU DK AT ES NL FR CZ PL HR LV
Global end of trial date	03 December 2019

Results information

Result version number	v1 (current)
This version publication date	05 August 2020
First version publication date	05 August 2020

Trial information

Trial identification

Sponsor protocol code	EMR100070-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02395172
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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	03 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to demonstrate superiority with regards to overall survival of Avelumab versus Docetaxel in subjects with programmed death ligand 1 (PD-L1) positive, non-small cell lung cancer (NSCLC) after failure of a platinum-based doublet.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 23
Country: Number of subjects enrolled	Australia: 5
Country: Number of subjects enrolled	Belgium: 26
Country: Number of subjects enrolled	Brazil: 26
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Chile: 22
Country: Number of subjects enrolled	Colombia: 6
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Estonia: 1
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Japan: 101
Country: Number of subjects enrolled	Latvia: 1

Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Peru: 13
Country: Number of subjects enrolled	Poland: 67
Country: Number of subjects enrolled	Korea, Republic of: 100
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 16
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 36
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 12
Country: Number of subjects enrolled	Turkey: 100
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	792
EEA total number of subjects	335

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)	426
From 65 to 84 years	361
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

First subject signed informed consent: 24 Mar 2015, Clinical data cut-off: 04 March 2019.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Avelumab

Arm description:

Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	MSB0010718C
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received intravenous infusion of avelumab at a dose of 10 mg/kg over the duration of 1 hour once every 2 weeks until confirmed disease progression.

Arm title	Docetaxel

Arm description:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression.

Number of subjects in period 1	Avelumab	Docetaxel
Started	396	396
Treated	393	365
Completed	393	365
Not completed	3	31
Subjects randomized but not treated	3	31

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab
Reporting group description:	
Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.	
Reporting group title	Docetaxel
Reporting group description:	
Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.	

Reporting group values	Avelumab	Docetaxel	Total
Number of subjects	396	396	792
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	62.8	62.5	
standard deviation	± 9.99	± 9.65	-
Sex: Female, Male Units: Subjects			
Female	127	123	250
Male	269	273	542
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	102	114	216
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	5	1	6
White	273	262	535
Not collected at the site	14	14	28
Other	1	4	5
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	59	42	101
Not Hispanic or Latino	297	307	604
Unknown or Not Reported	40	47	87

End points

End points reporting groups

Reporting group title	Avelumab

Reporting group description:

Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Reporting group title	Docetaxel

Reporting group description:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Primary: Overall Survival (OS) Time in Programmed Death Ligand 1 (PD-L1) + Full Analysis Set Population (FAS)

End point title	Overall Survival (OS) Time in Programmed Death Ligand 1 (PD-L1) + Full Analysis Set Population (FAS)

End point description:

The OS time was defined as the time from randomization to the date of death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subjects was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with greater than or equal to (>=) 1 percentage (%) of tumor cells with >=1+ positive membrane staining intensity for PD-L1 protein.

End point type	Primary

End point timeframe:

Time from date of randomization up to 1420 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: months				
median (confidence interval 95%)	11.4 (9.4 to 13.8)	10.6 (8.5 to 12.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis: OS in PD-L1 + FAS
Comparison groups	Avelumab v Docetaxel

Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0721
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.05

Secondary: Overall Survival (OS) Time in Full Analysis Set Population

End point title	Overall Survival (OS) Time in Full Analysis Set Population

End point description:

The OS time was defined as the time from randomization to the date of death. The subjects who were still alive at the time of data analysis or who were lost to follow-up OS time was censored at the last recorded date that the subjects was known to be alive before the data cutoff date. OS was measured using Kaplan-Meier (KM) estimates. Full analysis set (FAS) included all subjects who were randomized to study.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 1420 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: months				
median (confidence interval 95%)	10.6 (9.2 to 12.3)	9.9 (8.1 to 11.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis: OS in FAS
Comparison groups	Avelumab v Docetaxel
Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.05

Secondary: Progression-Free Survival (PFS) Time in PD-L1+ Full Analysis Set Population

End point title	Progression-Free Survival (PFS) Time in PD-L1+ Full Analysis Set Population

End point description:

PFS was defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as adjudicated by independent endpoint review committee (IERC). PD was defined as at least a 20 percent (%) increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. PFS was measured using Kaplan-Meier (KM) estimates. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with >= 1 percentage of tumor cells with >=1+ positive membrane staining intensity for PD-L1 protein.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: months				
median (confidence interval 95%)	3.4 (2.7 to 4.9)	4.1 (3.0 to 5.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis: PFS in PD-L1 + FAS
Comparison groups	Avelumab v Docetaxel
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.27

Secondary: Progression-Free Survival (PFS) Time in Full Analysis Set Population

End point title	Progression-Free Survival (PFS) Time in Full Analysis Set Population

End point description:

PFS was defined as the time from date of randomization until date of the first documentation of progressive disease (PD) or death due to any cause in the absence of documented PD, whichever occurs first. PFS was assessed as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) as adjudicated by independent endpoint review committee (IERC). PD was defined as at least a 20 percent (%) increase in the sum of longest diameter (SLD), taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions and unequivocal progression of non-target lesions. PFS was measured using Kaplan-Meier (KM) estimates. Full analysis set (FAS) included all subjects who were randomized to study.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: months				
median (confidence interval 95%)	2.8 (2.7 to 3.5)	4.2 (3.3 to 5.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis of PFS in FAS
Comparison groups	Avelumab v Docetaxel
Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.41

Secondary: Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by an Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

End point title	Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by an Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

End point description:

Confirmed BOR: best response of any of the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from the date of randomization until disease progression or recurrence (taking the smallest measurement recorded since the start of treatment as reference). CR: Disappearance of all evidence of target & non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD: a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions & unequivocal progression of non-target lesions. Number of subjects with best overall response in each category (CR, PR, SD, PD) was reported. FAS was used.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: subjects				
Complete Response	5	2		
Partial Response	54	42		
Stable Disease	129	158		
Non-complete Response/ Non-progressive Disease	5	13		
Progressive Disease	150	82		
Not Evaluable	53	99		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

End point title	Number of Subjects with Confirmed Best Overall Response (BOR) as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

End point description:

Confirmed BOR: best response of any of the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from the date of randomization until disease progression or recurrence (taking the smallest measurement recorded since the start of treatment as reference). CR: Disappearance of all evidence of target & non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD: a 20% increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions & unequivocal progression of non-target lesions. Number of subjects with best overall response in each category (CR, PR, SD, PD) was reported. PD-L1+FAS was used.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: subjects				
Complete Response	4	1		
Partial Response	46	30		
Stable Disease	86	104		
Non-complete Response/ Non-progressive Disease	4	12		
Progressive Disease	93	57		
Not Evaluable	31	61		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

End point title	Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in Full Analysis Set Population

End point description:

Percentage of subjects with objective response (CR plus PR) according to RECIST Version 1.1 was reported. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Full analysis set (FAS) included all subjects who were randomized to study.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	396		
Units: percentage of subjects				
number (confidence interval 95%)	14.9 (11.5 to 18.8)	11.1 (8.2 to 14.6)		

Statistical analyses

Statistical analysis title	Objective Response in FAS
Comparison groups	Avelumab v Docetaxel

Number of subjects included in analysis	792
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	2.13

Secondary: Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

End point title	Percentage of Subjects with Objective Response as Assessed by Independent Endpoint Review Committee (IERC) in PD-L1+ Full Analysis Set Population

End point description:

Percentage of subjects with objective response (CR plus PR) according to RECIST Version 1.1 was reported. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. PD-L1+ FAS included all PD-L1+ tumor subjects who were randomly assigned to trial treatment. The PD-L1+ subjects were with >= 1 percentage of tumor cells with >=1+ positive membrane staining intensity for PD-L1 protein.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 907 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	264	265		
Units: percentage of subjects				
number (confidence interval 95%)	18.9 (14.4 to 24.2)	11.7 (8.1 to 16.2)		

Statistical analyses

Statistical analysis title	Objective Response in PD-L1 + FAS
Comparison groups	Avelumab v Docetaxel
Number of subjects included in analysis	529
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.76

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.86

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End of Treatment (EOT)

End point title	Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Composite Index Score at End of Treatment (EOT)

End point description:

The EQ-5D-5L health outcome questionnaire was a measure of health status that provides a simple descriptive profile and a single index value. The EQ-5D-5L defined health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 items were combined to generate health profiles. These profiles were converted to a continuous single index score. The lowest possible score was -0.59 (unable to walk, unable to self-care, unable to do usual activities, extreme pain or discomfort, extreme anxiety or depression) and the highest score was 1.00 (no problems in all 5 dimensions). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "number of subjects analyzed" signified the subjects analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	196		
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1245 (± 0.28021)	-0.0988 (± 0.26615)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End of Treatment (EOT)

End point title	Change From Baseline in European Quality of Life 5-dimensions (EQ-5D-5L) Health Outcome Questionnaire Through Visual Analogue Scale (VAS) at End of Treatment (EOT)

End point description:

EQ-5D-5L was comprised of the following 5 participant-reported dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension had 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The responses were used to derive overall score using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 (worst health you can imagine) and 100 (best health you can imagine). Health-related quality of life

(HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "Number of subjects analyzed" signified the subjects analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171	196		
Units: millimeter				
arithmetic mean (standard deviation)	-8.1 (± 22.06)	-7.0 (± 21.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT)

End point title	Change From Baseline in European Organization for the Research and Treatment of Cancer Quality of Life (EORTC QLQ-C30) Global Health Status at End of Treatment (EOT)

End point description:

EORTC QLQ-C30 was a 30-question tool used to assess the overall quality of life (QoL) in cancer subjects. It consisted of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, role, cognitive, emotional, social), and 9 symptom scales/items (Fatigue, nausea and vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, financial impact). The EORTC QLQ-C30 GHS/QoL score ranged from 0 to 100, where 0 (very poor physical condition and QoL) and 100 (excellent overall physical condition and QoL). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "Number of subjects analyzed" signified the subjects analyzed in this endpoint.

End point type	Secondary

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172	196		
Units: units on a scale				
arithmetic mean (standard deviation)	-9.79 (± 24.506)	-9.44 (± 18.933)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT)

End point title	Change from Baseline in European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13) at End of Treatment (EOT)

End point description:

EORTC QLQ-LC13 consisted of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The EORTC QLQ-LC13 module generated one multiple-item scale assessing dyspnea, coughing, hemoptysis, sore mouth, dysphagia, neuropathy, alopecia, pain in chest, pain in arms or shoulder and pain in other parts. Score range: 0 (no burden of symptom domain or single symptom item) to 100 (highest burden of symptoms for symptom domains and single items). Health-related quality of life (HRQoL) analysis set was a subset of the FAS and includes all FAS subjects who had 1 baseline HRQoL assessment and at least 1 post-baseline HRQoL questionnaire completed. Here, "n" signified those subjects who were evaluable for the specified category.

End point type	Secondary

End point timeframe:

Baseline, End of treatment visit (up to Week 124)

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	348	333		
Units: units on a scale				
arithmetic mean (standard deviation)				
Dyspnea: (n = 172, 197)	9.95 (± 22.094)	8.52 (± 21.285)		
Coughing: (n = 172, 197)	-0.58 (± 30.263)	-2.03 (± 32.582)		
Hemoptysis: (n = 172, 197)	0.19 (± 14.191)	-0.34 (± 16.832)		
Sore Mouth: (n = 172, 197)	0.78 (± 17.643)	3.72 (± 24.920)		
Dysphagia: (n = 172, 197)	5.62 (± 18.401)	4.23 (± 21.538)		
Peripheral Neuropathy: (n = 172, 197)	0.19 (± 20.550)	9.81 (± 30.015)		
Alopecia: (n = 172, 197)	-3.10 (± 20.789)	30.80 (± 42.582)		
Pain in Chest: (n = 172, 197)	4.84 (± 28.993)	0.34 (± 26.935)		
Pain in Arm or Shoulder: (n = 172, 197)	5.62 (± 28.852)	0.85 (± 29.439)		
Pain in Other Parts: (n = 171, 197)	8.77 (± 34.410)	6.60 (± 30.978)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), Drug Related Treatment Emergent Adverse Events and Treatment Emergent Adverse Events Leading to Death

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs), Drug Related Treatment Emergent Adverse Events and Treatment Emergent Adverse Events Leading to Death

End point description:

An Adverse event (AE) was defined as any unfavorable and unintended sign (including clinically significant abnormal laboratory, vital signs and 12-lead Electrocardiogram findings), symptom, or disease temporally associated with the use of study drug or worsening of pre-existing medical condition, whether or not related to study drug. A serious adverse event (SAE) was an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in subject hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. Treatment-emergent events between first dose of study drug that were absent before treatment or that worsened relative to pre-treatment state up to 30 days after last administration. TEAEs included both Serious TEAEs and non-serious TEAEs. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 1420 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	365		
Units: subjects				
TEAEs	375	346		
TESAEs	167	145		
Drug Related TEAEs	252	313		
TEAEs Leading to Death	64	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs) by Severity

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs) by Severity

End point description:

Treatment Emergent Adverse Events were graded as per National Cancer Institute Common Terminology Criteria for Adverse Experience version 4.03 (NCI-CTCAE v 4.03). Grade 3 refers to severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care and Activity of daily living (ADL), Grade 4 refers to Life-threatening consequences; where urgent intervention indicated, Grade 5 refers to the death related to adverse event. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 1420 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	365		
Units: subjects				
Grade 3 or Higher	209	247		
Grade 4 or Higher	87	122		
Grade 5	63	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score vs. Worst Post-baseline Score

End point title	Number of Subjects with Eastern Cooperative Oncology Group (ECOG) Performance: Baseline Score vs. Worst Post-baseline Score

End point description:

ECOG performance status measured to assess subject's performance status on a scale of 0 to 5, where 0 = Fully active, able to carry on all pre-disease activities without restriction; 1 = Restricted in physically strenuous activity, ambulatory and able to carry out light or sedentary work; 2 = Ambulatory and capable of all selfcare but unable to carry out any work activities; 3 = Capable of only limited self-care, confined to bed/chair for more than 50 percent of waking hours; 4 = Completely disabled, cannot carry on any self-care, totally confined to bed/chair; 5 = dead. The subjects with missing worst post baseline score were also reported. ECOG performance status was reported in terms of number of subjects with Baseline value vs. worst post-baseline value (i.e. highest score) combination. Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 1420 days

End point values	Avelumab	Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	365		
Units: subjects				
Baseline score 0, worst post-baseline score 0	52	55		
Baseline score 0, worst post-baseline score 1	67	41		
Baseline score 0, worst post-baseline score 2	19	12		
Baseline score 0, worst post-baseline score 3	5	2		

Baseline score 0, worst post-baseline score 4	0	1		
Baseline score 0, worst post-baseline score 5	1	0		
Baseline score 0, worst post-baseline Missing	0	6		
Baseline score 1, worst post-baseline score 0	6	1		
Baseline score 1, worst post-baseline score 1	157	172		
Baseline score 1, worst post-baseline score 2	47	41		
Baseline score 1, worst post-baseline score 3	23	8		
Baseline score 1, worst post-baseline score 4	3	2		
Baseline score 1, worst post-baseline score 5	1	1		
Baseline score 1, worst post-baseline Missing	12	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NAbs) for Avelumab

End point title	Number of Subjects with Positive Anti-Drug Antibodies (ADAs) and Neutralizing Antibodies (NAbs) for Avelumab[1]

End point description:

Serum samples were analyzed by a validated electrochemiluminesce immunoassay to detect the presence of antidrug antibodies (ADA). Samples that screened positive were subsequently tested in a confirmatory assay were tested for neutralizing antibodies (nAb). Number of subjects with ADA or nAb positive results for Avelumab were reported. Full analysis set (FAS) included all subjects who were randomized to study. Here, "Number of Subjects Analyzed" signified subjects with at least on valid ADA result at any time point.

End point type	Secondary

End point timeframe:

Time from date of randomization up to 1420 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint was evaluated for Avelumab arm only.

End point values	Avelumab			
Subject group type	Reporting group			
Number of subjects analysed	388			
Units: subjects				
ADAs to Avelumab	58			
NAbs to Avelumab	14			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from date of randomization up to 1420 days

Adverse event reporting additional description:

Safety analysis set included all subjects who were administered at least 1 dose of the Investigational Medicinal Product.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Docetaxel

Reporting group description:

Subjects received 75 mg per square meter (m^2) (per label) of docetaxel by intravenous infusion once every 3 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Reporting group title	Avelumab

Reporting group description:

Subjects received 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous infusion once every 2 weeks until confirmed disease progression, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the study or Investigational Medicinal Product (IMP) as defined in the study protocol was fulfilled.

Serious adverse events	Docetaxel	Avelumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	145 / 365 (39.73%)	167 / 393 (42.49%)	
number of deaths (all causes)	297	316	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 365 (0.27%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			
subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			

subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour pain			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 365 (0.27%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			

subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (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	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	26 / 365 (7.12%)	41 / 393 (10.43%)	
occurrences causally related to treatment / all	0 / 26	0 / 41	
deaths causally related to treatment / all	0 / 20	0 / 32	
Asthenia			
subjects affected / exposed	3 / 365 (0.82%)	6 / 393 (1.53%)	
occurrences causally related to treatment / all	3 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	4 / 365 (1.10%)	6 / 393 (1.53%)	
occurrences causally related to treatment / all	1 / 4	0 / 6	
deaths causally related to treatment / all	1 / 4	0 / 6	
Pain			

subjects affected / exposed	1 / 365 (0.27%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 365 (0.82%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 365 (1.92%)	11 / 393 (2.80%)	
occurrences causally related to treatment / all	2 / 7	0 / 11	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pleural effusion			
subjects affected / exposed	3 / 365 (0.82%)	10 / 393 (2.54%)	
occurrences causally related to treatment / all	0 / 3	2 / 10	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 365 (0.82%)	6 / 393 (1.53%)	
occurrences causally related to treatment / all	1 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	1 / 365 (0.27%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	3 / 365 (0.82%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Haemoptysis			
subjects affected / exposed	4 / 365 (1.10%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Interstitial lung disease			
subjects affected / exposed	3 / 365 (0.82%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory failure			
subjects affected / exposed	3 / 365 (0.82%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 2	1 / 2	
Acute respiratory failure			
subjects affected / exposed	2 / 365 (0.55%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 365 (0.27%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asphyxia			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			

subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydrothorax			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophagobronchial fistula			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchial obstruction			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphonia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystic lung cancer			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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 / 365 (0.27%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	4 / 365 (1.10%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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			
Infusion related reaction			
subjects affected / exposed	0 / 365 (0.00%)	10 / 393 (2.54%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 365 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 365 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 365 (0.27%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute coronary syndrome			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune myocarditis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac failure			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiac tamponade			

subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Depressed level of consciousness			

subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Balance disorder			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurotoxicity			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			

subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	3 / 365 (0.82%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	2 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			

subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	22 / 365 (6.03%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	21 / 22	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 365 (0.82%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	10 / 365 (2.74%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	10 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 365 (0.27%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 365 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 365 (1.37%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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			
Angioedema			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Henoch-Schonlein purpura			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (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			
Acute kidney injury			
subjects affected / exposed	2 / 365 (0.55%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nephrolithiasis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Renal failure			

subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune thyroiditis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
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			
Back pain			
subjects affected / exposed	2 / 365 (0.55%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone pain			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (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			
Pneumonia			
subjects affected / exposed	19 / 365 (5.21%)	9 / 393 (2.29%)	
occurrences causally related to treatment / all	9 / 19	0 / 9	
deaths causally related to treatment / all	3 / 5	0 / 3	
Respiratory tract infection			
subjects affected / exposed	5 / 365 (1.37%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	2 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 365 (0.55%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 365 (0.55%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Appendicitis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural infection			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia streptococcal			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	4 / 365 (1.10%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Klebsiella infection			

subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (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	4 / 365 (1.10%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	5 / 365 (1.37%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	2 / 4	0 / 0	
Serratia infection			

subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 365 (0.27%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 365 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			

subjects affected / exposed	0 / 365 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 365 (0.27%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 365 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 365 (0.55%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	1 / 365 (0.27%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Docetaxel	Avelumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	307 / 365 (84.11%)	320 / 393 (81.42%)	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	66 / 365 (18.08%)	70 / 393 (17.81%)	
occurrences (all)	66	70	
Asthenia			
subjects affected / exposed	64 / 365 (17.53%)	55 / 393 (13.99%)	
occurrences (all)	64	55	
Pyrexia			
subjects affected / exposed	33 / 365 (9.04%)	50 / 393 (12.72%)	
occurrences (all)	33	50	
Chills			
subjects affected / exposed	3 / 365 (0.82%)	29 / 393 (7.38%)	
occurrences (all)	3	29	
Oedema peripheral			
subjects affected / exposed	37 / 365 (10.14%)	21 / 393 (5.34%)	
occurrences (all)	37	21	
Malaise			
subjects affected / exposed	26 / 365 (7.12%)	9 / 393 (2.29%)	
occurrences (all)	26	9	
Mucosal inflammation			
subjects affected / exposed	22 / 365 (6.03%)	5 / 393 (1.27%)	
occurrences (all)	22	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	46 / 365 (12.60%)	77 / 393 (19.59%)	
occurrences (all)	46	77	
Dyspnoea			
subjects affected / exposed	54 / 365 (14.79%)	75 / 393 (19.08%)	
occurrences (all)	54	75	
Productive cough			
subjects affected / exposed	8 / 365 (2.19%)	25 / 393 (6.36%)	
occurrences (all)	8	25	
Haemoptysis			

subjects affected / exposed	15 / 365 (4.11%)	25 / 393 (6.36%)	
occurrences (all)	15	25	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	22 / 365 (6.03%)	19 / 393 (4.83%)	
occurrences (all)	22	19	
Investigations			
Weight decreased			
subjects affected / exposed	30 / 365 (8.22%)	50 / 393 (12.72%)	
occurrences (all)	30	50	
Neutrophil count decreased			
subjects affected / exposed	34 / 365 (9.32%)	3 / 393 (0.76%)	
occurrences (all)	34	3	
White blood cell count decreased			
subjects affected / exposed	21 / 365 (5.75%)	2 / 393 (0.51%)	
occurrences (all)	21	2	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	8 / 365 (2.19%)	56 / 393 (14.25%)	
occurrences (all)	8	56	
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 365 (5.21%)	30 / 393 (7.63%)	
occurrences (all)	19	30	
Neuropathy peripheral			
subjects affected / exposed	33 / 365 (9.04%)	6 / 393 (1.53%)	
occurrences (all)	33	6	
Peripheral sensory neuropathy			
subjects affected / exposed	27 / 365 (7.40%)	3 / 393 (0.76%)	
occurrences (all)	27	3	
Dysgeusia			
subjects affected / exposed	23 / 365 (6.30%)	1 / 393 (0.25%)	
occurrences (all)	23	1	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	81 / 365 (22.19%)	50 / 393 (12.72%)	
occurrences (all)	81	50	
Neutropenia			
subjects affected / exposed	48 / 365 (13.15%)	2 / 393 (0.51%)	
occurrences (all)	48	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	57 / 365 (15.62%)	56 / 393 (14.25%)	
occurrences (all)	57	56	
Constipation			
subjects affected / exposed	43 / 365 (11.78%)	45 / 393 (11.45%)	
occurrences (all)	43	45	
Vomiting			
subjects affected / exposed	28 / 365 (7.67%)	38 / 393 (9.67%)	
occurrences (all)	28	38	
Diarrhoea			
subjects affected / exposed	67 / 365 (18.36%)	44 / 393 (11.20%)	
occurrences (all)	67	44	
Stomatitis			
subjects affected / exposed	42 / 365 (11.51%)	9 / 393 (2.29%)	
occurrences (all)	42	9	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	17 / 365 (4.66%)	33 / 393 (8.40%)	
occurrences (all)	17	33	
Pruritus			
subjects affected / exposed	13 / 365 (3.56%)	26 / 393 (6.62%)	
occurrences (all)	13	26	
Alopecia			
subjects affected / exposed	97 / 365 (26.58%)	3 / 393 (0.76%)	
occurrences (all)	97	3	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 365 (0.27%)	24 / 393 (6.11%)	
occurrences (all)	1	24	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	17 / 365 (4.66%)	47 / 393 (11.96%)	
occurrences (all)	17	47	
Arthralgia			
subjects affected / exposed	30 / 365 (8.22%)	27 / 393 (6.87%)	
occurrences (all)	30	27	
Musculoskeletal pain			
subjects affected / exposed	15 / 365 (4.11%)	25 / 393 (6.36%)	
occurrences (all)	15	25	
Pain in extremity			
subjects affected / exposed	12 / 365 (3.29%)	23 / 393 (5.85%)	
occurrences (all)	12	23	
Myalgia			
subjects affected / exposed	43 / 365 (11.78%)	17 / 393 (4.33%)	
occurrences (all)	43	17	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	12 / 365 (3.29%)	28 / 393 (7.12%)	
occurrences (all)	12	28	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	76 / 365 (20.82%)	79 / 393 (20.10%)	
occurrences (all)	76	79	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2015	- Added language regarding the predicted number of deaths due to NSCLC in the EU in 2014. - Added language to inclusion criterion 13 for subjects being treated with docetaxel to use effective contraception for up to 3 months after docetaxel treatment and to advise male subjects not to father a child during the 3 months after treatment with docetaxel and to seek advice on conservation of sperm prior to treatment.
10 July 2015	− Excluded further enrollment of NSCLC subjects with EGFR mutations. − Modified language in Exclusion criterion 4 such that prior therapy with cancer vaccine was no longer allowed. − Changed the duration of treatment for subjects with a confirmed CR to a maximum of 24 months. − Modified AE and SAE follow-up language such that subjects with an AE ongoing at the time of the End-of-Treatment visit must be followed up until the Safety follow-up visit and subjects with a SAE ongoing at the Long term follow-up visit must be followed up by the Investigator until stabilization or until outcome was known, unless the subject was documented as "lost to follow-up. − Changed the bilirubin inclusion criterion from 1.0 x ULN to 1.5 x ULN. − Modified hepatitis testing to include type of test. − Modified mandatory chest CT to allow MRI of the chest to account for regions where CT may be prohibited. − Added language stipulating that complete blood count and core chemistry samples must be drawn and results reviewed within 48 hours prior to IMP administration. − Deleted patient-reported outcome / quality-of-life assessments from the Safety Follow-up and Long-term Follow-up visits. − Added language allowing corticosteroid use in subjects randomized to docetaxel. − Added vaccines to the list of prohibited medications. − Added PK sampling at the End-of-Treatment visit and ADA sampling at the Safety Follow-up visit.
15 November 2016	− Increased the number of subject to be randomized in the study by 100 due to the new (lower) estimation of the proportion of subjects with PD-L1+ tumors and updated the proportion expected to have PD-L1+ tumors from 80% to 70%. − Updated language regarding tumor assessments so that after 1 year (Week 55) from the start of treatment, assessments would be every 12 weeks (rather than every 6 weeks). − Changed Human Antihuman Antibody (HAHA) to ADA throughout the protocol. − Corrected discrepancies in PK sampling between the text and the Schedule of Assessments − Updated contraception language in the Inclusion Criteria to harmonize with the rest of the avelumab program. − Deleted requirement for subjects with repeated Grade 2 IRRs and ADRs to be withdrawn from treatment. − Updated language on timing of when weight should be determined for dose calculation in order to give more flexibility to Investigators − Deleted bisphosphonate and denosumab from list of nonpermissible medications. − Added language to allow subjects with brain metastases to continue treatment if they fulfilled outlined criteria. − Added guidelines for the management of suspected cardiac-related Immune-related adverse event (irAEs). − Changed definition of overdose from >= 5% to >= 10% of calculated dose. − Deleted blood sample collection for Adrenocorticotropic hormone (ACTH), Antinuclear antibody (ANA), Antineutrophil cytoplasmic antibody (ANCA) and rheumatoid factor from End of Treatment and Safety Follow-up visits − Deleted the PP analysis set and any associated analyses − Replaced the ITT population with the FAS

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported