Clinical trial results:
A Phase III, Randomized, Double-blind, Placebo-controlled, Multi-center, International Study of durvalumab as Sequential Therapy in Patients with Locally Advanced, Unresectable Non-Small Cell Lung Cancer (Stage III) Who Have Not Progressed Following Definitive, Platinum-based, Concurrent Chemoradiation Therapy (PACIFIC)

Summary

EudraCT number	2014-000336-42
Trial protocol	SK IT DE HU GB ES NL BE PL GR
Global end of trial date	24 August 2023

Results information

Result version number	v1 (current)
This version publication date	18 October 2023
First version publication date	18 October 2023

Trial information

Trial identification

Sponsor protocol code	D4191C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02125461
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Södertälje, Södertälje, Sweden, SE 151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 8772409479, information.center@astrazeneca.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	11 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of durvalumab treatment compared with placebo in terms of overall survival (OS) and progression-free survival (PFS).

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation / Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy:

Patients must have received at least 2 cycles of platinum-based chemotherapy concurrent with radiation therapy, which must be completed within 1 to 42 days prior to randomization in the study.

Evidence for comparator: -

Actual start date of recruitment	09 May 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
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	France: 43
Country: Number of subjects enrolled	Spain: 61
Country: Number of subjects enrolled	Australia: 42
Country: Number of subjects enrolled	Turkey: 36
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Netherlands: 17
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Slovakia: 8
Country: Number of subjects enrolled	South Africa: 4
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 170

Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	Mexico: 11
Country: Number of subjects enrolled	Japan: 112
Country: Number of subjects enrolled	Korea, Republic of: 46
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Viet Nam: 3
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Peru: 3
Worldwide total number of subjects	713
EEA total number of subjects	226

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)	391
From 65 to 84 years	320
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients were randomized between 09 May 2014 and 22 Apr 2016 in 235 study centers across 26 countries. Data cut-off (DCO) date for analysis of PFS and PFS rates at 12 and 18 months: 13 Feb 2017; DCO date for analysis of OS and all other secondary endpoints: 22 Mar 2018; DCO date for study completion: 11 Jan 2021.

Pre-assignment

Screening details:

Eligible patients with locally advanced, unresectable Stage III non-small cell lung cancer were randomized in a 2:1 ratio to receive either durvalumab (MEDI4736) 10 milligrams (mg) / kilogram (kg) every 2 weeks (Q2W) or placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab (MEDI4736)

Arm description:

Patients in the durvalumab (MEDI4736) monotherapy group were to receive durvalumab 10 mg/kg Q2W via intravenous infusion for up to 12 months.

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	MEDI4736
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received durvalumab 10 mg/kg via intravenous infusion Q2W.

Arm title	Placebo

Arm description:

Patients in the placebo group were to receive matching placebo for intravenous infusion Q2W for up to 12 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received placebo matching durvalumab via intravenous infusion Q2W.

Number of subjects in period 1	Durvalumab (MEDI4736)	Placebo
Started	476	237
Full analysis set (FAS)	476	237
Received treatment	473	236
Safety analysis set	475	234
Completed 12 months of treatment	232	82
Completed	178	68
Not completed	298	169
Adverse event, serious fatal	260	149
Consent withdrawn by subject	30	16
Missing Termination Reason	-	1
Lost to follow-up	8	3

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab (MEDI4736)
Reporting group description:	
Patients in the durvalumab (MEDI4736) monotherapy group were to receive durvalumab 10 mg/kg Q2W via intravenous infusion for up to 12 months.	
Reporting group title	Placebo
Reporting group description:	
Patients in the placebo group were to receive matching placebo for intravenous infusion Q2W for up to 12 months.	

Reporting group values	Durvalumab (MEDI4736)	Placebo	Total
Number of subjects	476	237	713
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	215	105	320
From 65-84 years	261	130	391
85 years and over	0	2	2
Age Continuous Units: years			
arithmetic mean	63.0	62.6	
standard deviation	± 8.66	± 9.64	-
Sex: Female, Male Units: Subjects			
Female	142	71	213
Male	334	166	500
Smoking History Units: Subjects			
Non-smoker	43	21	64
Ex-smoker	354	178	532
Current smoker	79	38	117
Race/Ethnicity, Customized Units: Subjects			
White	337	157	494
Black or African American	12	2	14
Asian	120	72	192
Native Hawaiian or Pacific Islander	1	1	2
American Indian or Alaska Native	4	5	9
Other	1	0	1
Missing	1	0	1

End points

End points reporting groups

Reporting group title	Durvalumab (MEDI4736)
Reporting group description:	
Patients in the durvalumab (MEDI4736) monotherapy group were to receive durvalumab 10 mg/kg Q2W via intravenous infusion for up to 12 months.	
Reporting group title	Placebo
Reporting group description:	
Patients in the placebo group were to receive matching placebo for intravenous infusion Q2W for up to 12 months.	

Primary: Overall Survival

End point title	Overall Survival
End point description:	
OS was defined as the time from the date of randomization until death due to any cause. OS was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis.	
End point type	Primary
End point timeframe:	
From baseline until death due to any cause. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.	

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476[1]	237[2]		
Units: Months				
median (confidence interval 95%)	99999 (34.7 to 99999)	28.7 (22.9 to 99999)		

Notes:

[1] - 99999 denotes that the value was not calculable (not reached)

[2] - 99999 denotes that the value was not calculable (not reached)

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo
Statistical analysis description:	
Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.	
Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00251
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.87

Primary: Progression Free Survival based on Blinded Independent Central Review (BICR) according to response evaluation criteria in solid tumors (RECIST 1.1)

End point title	Progression Free Survival based on Blinded Independent Central Review (BICR) according to response evaluation criteria in solid tumors (RECIST 1.1)

End point description:

PFS was defined as the time from randomization until the date of objective disease progression (RECIST 1.1) or death (by any cause in the absence of progression). Progression was defined using RECIST 1.1 as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions. PFS was calculated using the Kaplan-Meier technique. The full analysis set (FAS) included all randomized patients, analyzed on an intent-to-treat (ITT) basis.

End point type	Primary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed until 13 Feb 2017 DCO; up to a maximum of approximately 3 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Months				
median (confidence interval 95%)	16.8 (13.0 to 18.1)	5.6 (4.6 to 7.8)		

Statistical analyses

Statistical analysis title	Durvalumab versus (vs) Placebo

Statistical analysis description:

Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Comparison groups	Placebo v Durvalumab (MEDI4736)
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.65

Secondary: Proportion of patients alive and progression free at 12 months from (APF12) based on BICR assessments according to RECIST 1.1

End point title	Proportion of patients alive and progression free at 12 months from (APF12) based on BICR assessments according to RECIST 1.1

End point description:

APF12 was defined as the percentage of patients who were alive and progression free per RECIST 1.1 at 12 months after randomization per Kaplan-Meier estimate of PFS at 12 months. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~ 12 weeks thereafter until confirmed disease progression. Assessed until 13 Feb 2017 DCO; up to a maximum of approximately 3 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Percentage of patients				
number (confidence interval 95%)	55.9 (51.0 to 60.4)	35.3 (29.0 to 41.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) based on BICR assesments according to RECIST 1.1

End point title	Objective Response Rate (ORR) based on BICR assesments according to RECIST 1.1

End point description:

ORR was defined as the percentage of patients with at least one visit response of Complete Response (CR) or Partial Response (PR) per RECIST 1.1 for target lesions: CR: Disappearance of all target lesions; PR: >=30% decrease in the sum of the longest diameter of target lesions; OR = CR + PR. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~ 12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	443	213		
Units: Percentage of patients				
number (confidence interval 95%)	30.0 (25.79 to 34.53)	17.8 (12.95 to 23.65)		

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo

Statistical analysis description:

Analysis performed using Fisher's exact test with mid p-value modification by subtracting half of the probability of the observed table from Fisher's p-value.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	656
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Fisher exact

Secondary: Duration of Response (DoR) based on BICR assessments according to RECIST 1.1

End point title	Duration of Response (DoR) based on BICR assessments according to RECIST 1.1

End point description:

DoR was defined as the time from date for first documented response of CR or PR until the first documented response of progression per RECIST 1.1 or death in the absence of progression. DoR was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis. Only patients with an objective response were included in the analysis.

End point type	Secondary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~ 12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[3]	38		
Units: Months				
median (confidence interval 95%)	99999 (27.4 to 99999)	18.4 (6.7 to 24.5)		

Notes:

[3] - 99999 denotes that the value was not calculable (not reached)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to death or distant metastasis (TTDM) based on BICR assessments according to RECIST 1.1

End point title	Time to death or distant metastasis (TTDM) based on BICR assessments according to RECIST 1.1

End point description:

TTDM was defined as the time from the date of randomization until the first date of distant metastasis or death in the absence of distant metastasis. Distant metastasis was defined as any new lesion that was outside of the radiation field according to RECIST 1.1 or proven by biopsy. TTDM was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~ 12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Months				
median (confidence interval 95%)	28.3 (24.0 to 34.9)	16.2 (12.5 to 21.1)		

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo

Statistical analysis description:

Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	0.68

Secondary: Proportion of patients alive and progression free at 18 months from (APF18) based on BICR assessments according to RECIST 1.1

End point title	Proportion of patients alive and progression free at 18 months from (APF18) based on BICR assessments according to RECIST 1.1

End point description:

APF18 was defined as the percentage of patients who were alive and progression free per RECIST 1.1 at 18 months after randomization per the Kaplan-Meier estimate of PFS at 18 months. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Tumor scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~ 12 weeks thereafter until confirmed disease progression. Assessed until 13 Feb 2017 DCO; up to a maximum of approximately 3 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Percentage of patients				
number (confidence interval 95%)	44.2 (37.7 to 50.5)	27.0 (19.9 to 34.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Alive at 24 Months (OS24)

End point title	Percentage of Patients Alive at 24 Months (OS24)

End point description:

OS24 was defined as the percentage of patients who were alive at 24 months after randomization per the Kaplan-Meier estimate of OS at 24 months. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

From baseline until death due to any cause. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Percentage of patients				
number (confidence interval 95%)	66.3 (61.7 to 70.4)	55.6 (48.9 to 61.8)		

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo
Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [4]
Method	z-test

Notes:

[4] - P-value based on z-test where z-test statistic is the ratio of the log-transformed ratio of the cumulative hazards in the 2 treatment arms divided by square root of the variance. Variance was estimated using the delta method and Greenwood's formula.

Secondary: Time to second progression or death (PFS2)

End point title	Time to second progression or death (PFS2)

End point description:

PFS2 was defined as the time from randomization to the time of the second progression or death. The date of second progression was recorded by the investigator and defined according to local standard clinical practice, and could have involved any of the following: objective radiological, symptomatic progression, or death. RECIST assessments were not collected for assessment of PFS2. PFS2 was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis.

End point type	Secondary

End point timeframe:

Following confirmed progression, patients were assessed every ~12 weeks until second disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Months				
median (confidence interval 95%)	28.3 (25.1 to 34.7)	17.1 (14.5 to 20.7)		

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo

Statistical analysis description:

Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.73

Secondary: Time to Deterioration of Global Health Status / Health-Related Quality of Life (HRQoL), Assessed Using European Organization for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30)

End point title	Time to Deterioration of Global Health Status / Health-Related Quality of Life (HRQoL), Assessed Using European Organization for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC QLQ-C30)

End point description:

Global health status/HRQoL was assessed using the EORTC QLQ-C30 global QoL scale which includes 2 items from the QLQ-C30: "How would you rate your overall health during the past week?" (Item 29) and "How would you rate your overall QoL during the past week?" (Item 30). Scores from 0 to 100 were derived for each item with higher scores indicating a better health status. Time to deterioration for global health status/HRQoL was defined as time from randomization until the date of first clinically meaningful deterioration (a decrease in global health status/HRQoL from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful deterioration. Time to deterioration was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis. Only patients with baseline scores ≥ 10 were included in the analysis.

End point type	Secondary

End point timeframe:

At baseline, every 4 weeks for first 8 weeks, then every ~8 weeks until 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476	237		
Units: Months				
median (confidence interval 95%)	7.4 (5.5 to 9.3)	5.7 (4.2 to 10.5)		

Statistical analyses

Statistical analysis title	Durvalumab vs Placebo

Statistical analysis description:

The hazard ratio and confidence interval (CI) were estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties, the stratification factors age at randomization (<65 vs ≥65), sex (male vs female) and smoking history (smoker vs non-smoker) in the strata statement, and the CI calculated using a profile likelihood approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.664 [5]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.18

Notes:

[5] - Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Secondary: Time to Deterioration of Primary Patient-Reported Outcome (PRO) Symptoms, Assessed Using European Organization for Research and Treatment of Cancer QoL lung cancer module (EORTC QLQ-LC13)

End point title	Time to Deterioration of Primary Patient-Reported Outcome (PRO) Symptoms, Assessed Using European Organization for Research and Treatment of Cancer QoL lung cancer module (EORTC QLQ-LC13)

End point description:

The EORTC QLQ-LC13 is a lung cancer specific module from the EORTC comprising 13 questions to assess lung cancer symptoms, treatment related side-effects and pain medication. Scores from 0 to 100 were derived for each symptom item with higher scores representing greater symptom severity. Time to symptom deterioration was defined as time from randomization until date of first clinically meaningful symptom deterioration (an increase in the score from baseline of ≥10) or death (by any cause) in the absence of a clinically meaningful symptom deterioration. Results are presented for time to deterioration in the following PRO endpoints identified as primary for EORTC QLQ-LC13: dyspnea, cough, hemoptysis and chest pain. Time to deterioration was calculated using the Kaplan-Meier technique. The FAS included all randomized patients, analyzed on an ITT basis. Only patients with baseline scores ≤ 90 were included in the analysis. 'n' denotes number of patients analyzed for each category.

End point type	Secondary

End point timeframe:

At baseline, every 4 weeks for first 8 weeks, then every ~8 weeks until 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed until 22 Mar 2018 DCO; up to a maximum of approximately 4 years.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	476[6]	237[7]		
Units: Months				
median (confidence interval 95%)				
Dyspnea (n=467, 230)	2.8 (1.9 to 3.7)	3.7 (2.3 to 4.1)		
Cough (n=442, 216)	5.6 (4.5 to 7.3)	5.6 (3.7 to 6.0)		
Hemoptysis (n=472, 232)	99999 (99999 to 99999)	29.6 (21.2 to 99999)		
Chest pain (n=463, 229)	11.1 (7.4 to 18.6)	8.3 (5.6 to 13.8)		

Notes:

[6] - 99999 denotes that the value was not calculable (not reached)

[7] - 99999 denotes that the value was not calculable (not reached)

Statistical analyses

Statistical analysis title	Dyspnea: Durvalumab vs Placebo

Statistical analysis description:

The hazard ratio and CI were estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties, the stratification factors age at randomization (<65 vs ≥65), sex (male vs female) and smoking history (smoker vs non-smoker) in the strata statement, and the CI calculated using a profile likelihood approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.522 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.29

Notes:

[8] - Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Statistical analysis title	Chest Pain: Durvalumab vs Placebo

Statistical analysis description:

The hazard ratio and CI were estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties, the stratification factors age at randomization (<65 vs ≥65), sex (male vs female) and smoking history (smoker vs non-smoker) in the strata statement, and the CI calculated using a profile likelihood approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.626 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.19

Notes:

[9] - Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Statistical analysis title	Hemoptysis: Durvalumab vs Placebo

Statistical analysis description:

Treatment comparison for hemoptysis. The hazard ratio and CI were estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties, the stratification factors age at randomization (<65 vs ≥65), sex (male vs female) and smoking history (smoker vs non-smoker) in the strata statement, and the CI calculated using a profile likelihood approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.048 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1

Notes:

[10] - Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Statistical analysis title	Cough: Durvalumab vs Placebo

Statistical analysis description:

The hazard ratio and CI were estimated from a stratified Cox proportional hazards model with the Breslow method to control for ties, the stratification factors age at randomization (<65 vs ≥65), sex (male vs female) and smoking history (smoker vs non-smoker) in the strata statement, and the CI calculated using a profile likelihood approach.

Comparison groups	Durvalumab (MEDI4736) v Placebo
Number of subjects included in analysis	713
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.38 [11]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.12

Notes:

[11] - Analysis performed using a stratified log rank test adjusting for age at randomization (<65 vs ≥65), sex (male vs female), and smoking history (smoker vs non-smoker) with ties handled using the Breslow approach.

Secondary: Number of Patients with Anti-Drug Antibody (ADA) Response to Durvalumab

End point title	Number of Patients with Anti-Drug Antibody (ADA) Response to Durvalumab

End point description:

ADA positive post-baseline only was also referred to as treatment-induced ADA positive. Treatment-boosted ADA was defined as baseline positive ADA titer that was boosted by ≥4-fold following drug administration. Persistently positive was defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment. Transiently positive was defined as having at least 1 post-baseline ADA positive assessment and not fulfilling the conditions of persistently positive. Confirmed ADA positive samples were subsequently tested in a neutralizing antibody assay. The ADA evaluable population included patients who had non-missing baseline ADA and at least 1 non-missing post-baseline ADA results.

End point type	Secondary

End point timeframe:

Samples were collected pre-dose on Day 1 (Week 0), Week 8, Week 24 and Week 48. Analysis performed at 22 Mar 2018 DCO.

End point values	Durvalumab (MEDI4736)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	416	204		
Units: Patients				
ADA positive at any visit	19	10		
ADA positive post-baseline only	8	5		
Treatment-boosted ADA positive	0	0		
ADA positive at baseline and post-baseline	2	2		
ADA positive at baseline only	9	3		
ADA persistently positive	5	5		
ADA transient positive	5	2		
Neutralizing antibodies positive at any visit	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of Durvalumab; Peak and Trough Serum concentrations

End point title	Pharmacokinetics (PK) of Durvalumab; Peak and Trough Serum concentrations[12]

End point description:

To evaluate PK, blood samples were collected pre-dose and post-dose and trough and peak serum concentrations of durvalumab, respectively, were determined. Pre-dose samples were taken within 60 minutes before infusion and post-dose samples were taken within 10 minutes after the end of infusion. The PK analysis set included all patients who received at least 1 dose of durvalumab per the protocol,

for whom any post-dose data were available, and who did not violate or deviate from the protocol in ways that would significantly affect the PK analyses. 'n' denotes number of patients analyzed for each category.

End point type	Secondary

End point timeframe:

Samples were collected pre-dose on Day 1 (Week 0), Week 8, Week 24 and Week 48, and post-dose on Day 1 (Week 0) and Week 24. Analysis performed at 22 Mar 2018 DCO.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point is reporting PK data for durvalumab and therefore reporting results for the placebo arm is not applicable.

End point values	Durvalumab (MEDI4736)			
Subject group type	Reporting group			
Number of subjects analysed	473			
Units: Micrograms per milliliter				
geometric mean (geometric coefficient of variation)				
Week 0: peak concentration (n=385)	191.00 (± 72.4)			
Week 8: trough concentration (n=289)	120.00 (± 62.2)			
Week 24: trough concentration (n=225)	177.00 (± 47.9)			
Week 24: peak concentration (n=207)	373.00 (± 43.6)			
Week 48: trough concentration (n=213)	186.00 (± 67.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious and non-serious treatment-emergent adverse event (TEAE) data collected during the 12-month treatment period. Deaths (all causes) collected for entire duration of the study. Assessed until 11 Jan 2021 DCO for study completion.

Adverse event reporting additional description:

TEAEs include events from first dose of study drug until earlier of 90 days after last dose or date of first subsequent therapy. 473 and 236 patients in durvalumab and placebo groups, respectively, received treatment but 2 patients randomized to placebo received 1 dose of durvalumab in error and are included in the durvalumab safety analysis set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients in the placebo group were to receive matching placebo for intravenous infusion Q2W for up to 12 months.

Reporting group title	Durvalumab (MEDI4736)

Reporting group description:

Patients in the durvalumab (MEDI4736) monotherapy group were to receive durvalumab 10 mg/kg Q2W via intravenous infusion for up to 12 months.

Serious adverse events	Placebo	Durvalumab (MEDI4736)	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 234 (23.08%)	138 / 475 (29.05%)	
number of deaths (all causes)	154	262	
number of deaths resulting from adverse events	15	21	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Giant cell tumour of tendon sheath			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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 / 234 (0.00%)	1 / 475 (0.21%)	
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	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral ischaemia			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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			
Mucosal inflammation			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Fatigue			
subjects affected / exposed	2 / 234 (0.85%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Calculus prostatic			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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			
Haemoptysis			
subjects affected / exposed	1 / 234 (0.43%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchial obstruction			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute interstitial pneumonitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopleural fistula			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory distress			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	1 / 234 (0.43%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	7 / 234 (2.99%)	17 / 475 (3.58%)	
occurrences causally related to treatment / all	5 / 8	18 / 18	
deaths causally related to treatment / all	2 / 3	4 / 4	
Pneumonia aspiration			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 234 (0.85%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 234 (0.00%)	5 / 475 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Myocardial necrosis marker increased			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ejection fraction decreased			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain natriuretic peptide increased			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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			
Radiation oesophagitis			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	4 / 234 (1.71%)	17 / 475 (3.58%)	
occurrences causally related to treatment / all	0 / 5	4 / 17	
deaths causally related to treatment / all	0 / 1	1 / 1	
Post procedural fistula			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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	0 / 234 (0.00%)	3 / 475 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 234 (0.43%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrioventricular block complete			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 234 (0.00%)	5 / 475 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriospasm coronary			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eosinophilic myocarditis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 234 (0.00%)	3 / 475 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular hole			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain upper			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 234 (0.85%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhoids			

subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Glomerulonephritis membranous			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular acidosis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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 / 234 (0.00%)	3 / 475 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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			
Septic shock			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	2 / 234 (0.85%)	4 / 475 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pneumonia pneumococcal			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia necrotising			
subjects affected / exposed	2 / 234 (0.85%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia adenoviral			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 234 (5.98%)	33 / 475 (6.95%)	
occurrences causally related to treatment / all	1 / 16	5 / 39	
deaths causally related to treatment / all	0 / 3	0 / 1	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall abscess			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotoxaemia			

subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
West Nile viral infection			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 234 (0.00%)	2 / 475 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 234 (0.00%)	3 / 475 (0.63%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			

subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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 bacterial			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
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 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 234 (0.43%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Iron overload			
subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			

subjects affected / exposed	0 / 234 (0.00%)	1 / 475 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	1 / 234 (0.43%)	0 / 475 (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	Placebo	Durvalumab (MEDI4736)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	212 / 234 (90.60%)	436 / 475 (91.79%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 234 (3.42%)	26 / 475 (5.47%)	
occurrences (all)	8	29	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	22 / 234 (9.40%)	70 / 475 (14.74%)	
occurrences (all)	23	92	
Oedema peripheral			
subjects affected / exposed	9 / 234 (3.85%)	37 / 475 (7.79%)	
occurrences (all)	10	41	
Non-cardiac chest pain			
subjects affected / exposed	21 / 234 (8.97%)	35 / 475 (7.37%)	
occurrences (all)	22	39	
Fatigue			
subjects affected / exposed	47 / 234 (20.09%)	114 / 475 (24.00%)	
occurrences (all)	52	130	
Asthenia			

subjects affected / exposed	31 / 234 (13.25%)	51 / 475 (10.74%)	
occurrences (all)	50	73	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	59 / 234 (25.21%)	169 / 475 (35.58%)	
occurrences (all)	75	220	
Dyspnoea			
subjects affected / exposed	57 / 234 (24.36%)	106 / 475 (22.32%)	
occurrences (all)	67	133	
Productive cough			
subjects affected / exposed	19 / 234 (8.12%)	46 / 475 (9.68%)	
occurrences (all)	26	53	
Pneumonitis			
subjects affected / exposed	11 / 234 (4.70%)	44 / 475 (9.26%)	
occurrences (all)	11	46	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	17 / 234 (7.26%)	45 / 475 (9.47%)	
occurrences (all)	18	47	
Injury, poisoning and procedural complications			
Radiation pneumonitis			
subjects affected / exposed	33 / 234 (14.10%)	80 / 475 (16.84%)	
occurrences (all)	33	84	
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 234 (9.40%)	33 / 475 (6.95%)	
occurrences (all)	25	36	
Headache			
subjects affected / exposed	21 / 234 (8.97%)	52 / 475 (10.95%)	
occurrences (all)	23	58	
Paraesthesia			
subjects affected / exposed	12 / 234 (5.13%)	22 / 475 (4.63%)	
occurrences (all)	13	24	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	26 / 234 (11.11%)	35 / 475 (7.37%)	
occurrences (all)	32	39	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	20 / 234 (8.55%)	57 / 475 (12.00%)	
occurrences (all)	27	59	
Diarrhoea			
subjects affected / exposed	46 / 234 (19.66%)	87 / 475 (18.32%)	
occurrences (all)	56	136	
Vomiting			
subjects affected / exposed	19 / 234 (8.12%)	36 / 475 (7.58%)	
occurrences (all)	25	45	
Nausea			
subjects affected / exposed	31 / 234 (13.25%)	68 / 475 (14.32%)	
occurrences (all)	43	88	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	12 / 234 (5.13%)	37 / 475 (7.79%)	
occurrences (all)	12	38	
Pruritus			
subjects affected / exposed	14 / 234 (5.98%)	60 / 475 (12.63%)	
occurrences (all)	17	70	
Rash			
subjects affected / exposed	18 / 234 (7.69%)	61 / 475 (12.84%)	
occurrences (all)	23	72	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 234 (1.71%)	54 / 475 (11.37%)	
occurrences (all)	4	62	
Hyperthyroidism			
subjects affected / exposed	4 / 234 (1.71%)	35 / 475 (7.37%)	
occurrences (all)	4	39	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	44 / 234 (18.80%)	83 / 475 (17.47%)	
occurrences (all)	49	110	

Myalgia			
subjects affected / exposed	10 / 234 (4.27%)	38 / 475 (8.00%)	
occurrences (all)	13	41	
Musculoskeletal chest pain			
subjects affected / exposed	18 / 234 (7.69%)	25 / 475 (5.26%)	
occurrences (all)	21	27	
Back pain			
subjects affected / exposed	27 / 234 (11.54%)	50 / 475 (10.53%)	
occurrences (all)	31	55	
Pain in extremity			
subjects affected / exposed	14 / 234 (5.98%)	31 / 475 (6.53%)	
occurrences (all)	14	35	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	24 / 234 (10.26%)	57 / 475 (12.00%)	
occurrences (all)	30	69	
Bronchitis			
subjects affected / exposed	19 / 234 (8.12%)	33 / 475 (6.95%)	
occurrences (all)	22	44	
Urinary tract infection			
subjects affected / exposed	13 / 234 (5.56%)	28 / 475 (5.89%)	
occurrences (all)	13	42	
Pneumonia			
subjects affected / exposed	12 / 234 (5.13%)	48 / 475 (10.11%)	
occurrences (all)	14	54	
Nasopharyngitis			
subjects affected / exposed	14 / 234 (5.98%)	42 / 475 (8.84%)	
occurrences (all)	18	51	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	12 / 234 (5.13%)	24 / 475 (5.05%)	
occurrences (all)	18	33	
Decreased appetite			
subjects affected / exposed	29 / 234 (12.39%)	69 / 475 (14.53%)	
occurrences (all)	32	84	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2014	The protocol was updated to add text to indicate study treatment should be discontinued if there is confirmed progression of disease following a previous response to study treatment.
08 August 2014	The protocol was updated to: • Add an interim analysis for PFS. • Reduce the frequency of specified study procedures and assessments following a review of the existing maturing Phase I safety database. • Increase the frequency of hematology and serum chemistry assessments and biomarkers; add the option of a 24-hour urine collection; and add assessments of temperature, respiratory rate and oxygen saturation for consistency with concurrent durvalumab studies. • Add justification for retreatment with durvalumab. • Update the criteria for Hy's Law. • Add secondary objectives and outcome measures for time to relapse and time to death or distant metastasis. • Remove text for duration of response evaluation.
18 February 2015	The protocol was updated to: • Allow patients a longer time period for resolution of toxicities from concurrent chemoradiation. • Clarify requirements regarding the chemoradiation therapy schedule and radiotherapy dose given. • Update an exclusion criterion, allowing patients with Grade 1 asymptomatic pneumonitis to participate in the study. • Update an inclusion criterion for adequate organ and marrow function to align with available clinical data and recommendations for the program.
11 February 2016	The protocol was updated to: • Remove time to relapse from study assessments. • Revise "Investigator site" assessments to "BICR" assessments. • Add an additional OS interim analysis. • Change the alpha level between PFS and OS for statistical testing of the co-primary endpoints. Additional adjustments were made with respect to the multiple testing procedures for controlling the Type I error rate. • Change the timing of the PFS interim analysis to a later time point. • Include additional laboratory parameters to table of assessments (amylase and lipase). • Clarify how a patient's weight is to be indicated for dosing calculations. • Update the list of potential adverse events of special interest (AESIs). • Update the clinically meaningful change in baseline score for EORTC QLQ-LC13. • Revise the PRO endpoints identified as primary for EORTC QLQ-LC13.
09 October 2017	The protocol was updated to: • Clarify requirements for independent data monitoring committee reviews. • Update retreatment criteria to allow patients to receive maximum benefit from treatment, and update guidance to Investigators for treatment and data collection for these patients. • Revise an Appendix to match updated toxicity management guidelines from August 2016.

07 December 2017	The protocol was updated to: • Revise an Appendix to match updated toxicity management guidelines from November 2017. • Update the list of potential AESIs. • Updated the study timetable and end-of-study procedures to clarify the circumstances under which the study may continue.
04 September 2019	The protocol was updated to: • Extend the estimated study completion date from Q3 2019 to Q2 2021 for the purposes of long-term follow-up. • Clarify that both primary analyses have been performed. • Amend the table of assessments, including removal of quality of life scales, removal of specified sampling and reducing frequency of scans. • Add mandatory biopsy requirement for entering retreatment. • Clarify availability of retreatment following the final DCO. • Clarify that survival follow-up will be completed upon completion of this protocol.

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.

Results of interim PFS analysis are considered as final PFS analysis; results of interim OS analysis are considered as final OS analysis. Patients were followed up for long-term survival until approximately 5 years after last patient enrolled.

Notes: