



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, Monitor, Data analyst, Carer, Assessor |

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: 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 |

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 |

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

| | |
|-----------------|---|
| End point title | Objective Response Rate (ORR) based on BICR assessments 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: $\geq 30\%$ 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: 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: 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: 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: 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

| 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: 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

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-booster 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-booster 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

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 occurrences (all) | 31 / 234 (13.25%) 50 | 51 / 475 (10.74%) 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 occurrences (all) | 26 / 234 (11.11%) 32 | 35 / 475 (7.37%) 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 occurrences (all) | 10 / 234 (4.27%) 13 | 38 / 475 (8.00%) 41 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 18 / 234 (7.69%) 21 | 25 / 475 (5.26%) 27 | |
| Back pain subjects affected / exposed occurrences (all) | 27 / 234 (11.54%) 31 | 50 / 475 (10.53%) 55 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 14 / 234 (5.98%) 14 | 31 / 475 (6.53%) 35 | |
| Infections and infestations | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 24 / 234 (10.26%) 30 | 57 / 475 (12.00%) 69 | |
| Bronchitis subjects affected / exposed occurrences (all) | 19 / 234 (8.12%) 22 | 33 / 475 (6.95%) 44 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 13 / 234 (5.56%) 13 | 28 / 475 (5.89%) 42 | |
| Pneumonia subjects affected / exposed occurrences (all) | 12 / 234 (5.13%) 14 | 48 / 475 (10.11%) 54 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 14 / 234 (5.98%) 18 | 42 / 475 (8.84%) 51 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 12 / 234 (5.13%) 18 | 24 / 475 (5.05%) 33 | |
| Decreased appetite subjects affected / exposed occurrences (all) | 29 / 234 (12.39%) 32 | 69 / 475 (14.53%) 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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 | <p>The protocol was updated to:</p> <ul style="list-style-type: none"> • 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 | <p>The protocol was updated to:</p> <ul style="list-style-type: none"> • 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: