



Clinical trial results:

A Phase III, Open-label, Randomized, Multi-center, International Study of MEDI4736, Given as Monotherapy or in Combination with Tremelimumab, Determined by PD-L1 Expression, Versus Standard of Care in Patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer (Stage IIIB-IV) Who Have Received At Least Two Prior Systemic Treatment Regimens Including One Platinum-based Chemotherapy Regimen and Do Not Have Known EGFR TK Activating Mutations or ALK Rearrangements (ARCTIC)

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2014-000338-46 |
| Trial protocol | DE GB ES BE GR HU NL CZ PL IT |
| Global end of trial date | 30 August 2023 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 10 August 2024 |
| First version publication date | 10 August 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D4191C00004 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02352948 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AstraZeneca |
| Sponsor organisation address | Alderley Park, Macclesfield, Cheshire, United Kingdom, SK10 4TG |
| Public contact | Medical Science Director, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@astrazeneca.com |
| Scientific contact | Medical Science Director, AstraZeneca, +1 302 885 1180, ClinicalTrialTransparency@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 | 09 February 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 February 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 August 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Sub-study A [Programmed cell death ligand 1 (PD-L1) high population]: To assess the efficacy of durvalumab monotherapy compared with standard of care (SoC) in terms of overall survival (OS) and progression-free survival (PFS).

Sub-study B (PD-L1 low/neg population): To assess the efficacy of durvalumab in combination with tremelimumab treatment compared with SoC in terms of OS and 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 Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 13 January 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Bulgaria: 7 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Chile: 6 |
| Country: Number of subjects enrolled | Czechia: 1 |
| Country: Number of subjects enrolled | France: 31 |
| Country: Number of subjects enrolled | Germany: 53 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Hong Kong: 2 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | Italy: 48 |
| Country: Number of subjects enrolled | Japan: 112 |
| Country: Number of subjects enrolled | Netherlands: 5 |
| Country: Number of subjects enrolled | Poland: 31 |
| Country: Number of subjects enrolled | Korea, Republic of: 29 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Romania: 11 |
| Country: Number of subjects enrolled | Russian Federation: 32 |
| Country: Number of subjects enrolled | Serbia: 18 |
| Country: Number of subjects enrolled | Singapore: 14 |
| Country: Number of subjects enrolled | Spain: 64 |
| Country: Number of subjects enrolled | Taiwan: 6 |
| Country: Number of subjects enrolled | Thailand: 11 |
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Country: Number of subjects enrolled | United States: 55 |
| Worldwide total number of subjects | 595 |
| EEA total number of subjects | 282 |

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) | 318 |
| From 65 to 84 years | 277 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was divided into 2 parts, sub-study A (82 centers across Europe, Asia, and North America) and sub-study B (149 centers across Europe, Asia, North America, and South America) conducted between 13 January 2015 and 09 February 2018 (data cut-off date).

Pre-assignment

Screening details:

The study had a pre-screening period to determine the programmed cell death ligand 1 (PD-L1) status, followed by a screening period and 12 month treatment period. A total of 595 participants were randomized to either sub-study A [PD-L1 high ($\geq 25\%$ of tumor cell (TC) expressing PD-L1)] or sub-study B [PD-L1 low/neg ($< 25\%$ of TC expressing PD-L1)].

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Sub-study A: Durvalumab |

Arm description:

Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses).

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

Dosage and administration details:

Durvalumab 10 mg/kg IV infusion Q2W for 12 months.

| | |
|------------------|------------------|
| Arm title | Sub-study A: SoC |
|------------------|------------------|

Arm description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m^2) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/ m^2 IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib 150 mg orally once daily.

| | |
|--|-----------------------|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |

| | |
|--|--------------------------------------|
| Routes of administration | Intravenous use |
| Dosage and administration details: Vinorelbine 30 mg/m ² IV on Days 1, 8, 15, and 22 of a 28-day cycle. | |
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of a 28-day cycle. | |
| Arm title | Sub-study B: Durvalumab+Tremelimumab |
| Arm description: Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses). | |
| Arm type | Experimental |
| Investigational medicinal product name | Tremelimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Tremelimumab 1 mg/kg IV infusion Q4W for 12 weeks. | |
| Investigational medicinal product name | Durvalumab |
| Investigational medicinal product code | MEDI4736 |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Durvalumab 20 mg/kg IV infusion Q4W for 12 weeks followed by durvalumab 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16. | |
| Arm title | Sub-study B: SoC |
| Arm description: Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: Erlotinib 150 mg orally once daily. | |
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of a 28-day cycle. | |

| | |
|--|-----------------------|
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Vinorelbine 30 mg/m² IV on Days 1, 8, 15, and 22 of a 28-day cycle.

| | |
|------------------|-------------------------|
| Arm title | Sub-study B: Durvalumab |
|------------------|-------------------------|

Arm description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

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

Dosage and administration details:

Durvalumab 10 mg/kg IV infusion Q2W for 12 months.

| | |
|------------------|---------------------------|
| Arm title | Sub-study B: Tremelimumab |
|------------------|---------------------------|

Arm description:

Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses).

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tremelimumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by Q12W for 24 weeks.

| Number of subjects in period 1 | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab |
|------------------------------------|-------------------------|------------------|--------------------------------------|
| | | | |
| Started | 62 | 64 | 174 |
| Received treatment | 62 | 63 | 173 |
| Completed study treatment | 15 | 0 ^[1] | 36 ^[2] |
| Completed | 13 | 5 | 45 |
| Not completed | 49 | 59 | 129 |
| Adverse event, serious fatal | 47 | 48 | 114 |
| Consent withdrawn by subject | 1 | 10 | 11 |
| Eligibility criteria not fulfilled | - | 1 | - |
| Unspecified | - | - | 2 |
| Lost to follow-up | 1 | - | 2 |

| Number of subjects in period 1 | Sub-study B: SoC | Sub-study B: Durvalumab | Sub-study B: Tremelimumab |
|--------------------------------|------------------|-------------------------|---------------------------|
|--------------------------------|------------------|-------------------------|---------------------------|

| | | | |
|------------------------------------|------------------|-------------------|------------------|
| Started | 118 | 117 | 60 |
| Received treatment | 110 | 117 | 60 |
| Completed study treatment | 0 ^[3] | 23 ^[4] | 4 ^[5] |
| Completed | 19 | 29 | 11 |
| Not completed | 99 | 88 | 49 |
| Adverse event, serious fatal | 74 | 77 | 44 |
| Consent withdrawn by subject | 23 | 9 | 4 |
| Eligibility criteria not fulfilled | 1 | - | - |
| Unspecified | - | - | - |
| Lost to follow-up | 1 | 2 | 1 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: It was not necessary for patients to complete the study treatment in order to complete the study

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Sub-study A: Durvalumab |
| Reporting group description: | |
| Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses). | |
| Reporting group title | Sub-study A: SoC |
| Reporting group description: | |
| Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m ²) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred. | |
| Reporting group title | Sub-study B: Durvalumab+Tremelimumab |
| Reporting group description: | |
| Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses). | |
| Reporting group title | Sub-study B: SoC |
| Reporting group description: | |
| Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred. | |
| Reporting group title | Sub-study B: Durvalumab |
| Reporting group description: | |
| Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses). | |
| Reporting group title | Sub-study B: Tremelimumab |
| Reporting group description: | |
| Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses). | |

| Reporting group values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab |
|---|-------------------------|------------------|--------------------------------------|
| Number of subjects | 62 | 64 | 174 |
| Age, Customized | | | |
| Units: Subjects | | | |
| <50 years | 3 | 11 | 16 |
| >=50 to <65 years | 31 | 25 | 79 |
| >=65 to <75 years | 24 | 21 | 64 |
| >=75 years | 4 | 7 | 15 |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 20 | 16 | 59 |
| Male | 42 | 48 | 115 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 22 | 23 | 41 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |

| | | | |
|---------------------------|----|----|-----|
| Black or African American | 0 | 1 | 3 |
| White | 40 | 40 | 129 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Other | 0 | 0 | 1 |

| Reporting group values | Sub-study B: SoC | Sub-study B: Durvalumab | Sub-study B: Tremelimumab |
|---|------------------|-------------------------|---------------------------|
| Number of subjects | 118 | 117 | 60 |
| Age, Customized Units: Subjects | | | |
| <50 years | 8 | 13 | 4 |
| >=50 to <65 years | 49 | 52 | 27 |
| >=65 to <75 years | 50 | 39 | 24 |
| >=75 years | 11 | 13 | 5 |
| Sex: Female, Male Units: Subjects | | | |
| Female | 37 | 44 | 21 |
| Male | 81 | 73 | 39 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 41 | 34 | 16 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 2 | 2 | 1 |
| White | 74 | 79 | 43 |
| Unknown or Not Reported | 0 | 1 | 0 |
| Other | 1 | 1 | 0 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 595 | | |
| Age, Customized Units: Subjects | | | |
| <50 years | 55 | | |
| >=50 to <65 years | 263 | | |
| >=65 to <75 years | 222 | | |
| >=75 years | 55 | | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 197 | | |
| Male | 398 | | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaska Native | 0 | | |
| Asian | 177 | | |
| Native Hawaiian or Other Pacific Islander | 0 | | |
| Black or African American | 9 | | |
| White | 405 | | |
| Unknown or Not Reported | 1 | | |
| Other | 3 | | |

End points

End points reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Sub-study A: Durvalumab |
| Reporting group description: Participants received durvalumab 10 milligrams per kilogram (mg/kg) intravenous (IV) infusion every 2 weeks (Q2W) for 12 months (up to 26 doses). | |
| Reporting group title | Sub-study A: SoC |
| Reporting group description: Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/meter square (m ²) IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until progression of disease (PD), initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred. | |
| Reporting group title | Sub-study B: Durvalumab+Tremelimumab |
| Reporting group description: Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion every 4 weeks (Q4W) for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses). | |
| Reporting group title | Sub-study B: SoC |
| Reporting group description: Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m ² IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m ² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anti-cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred. | |
| Reporting group title | Sub-study B: Durvalumab |
| Reporting group description: Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses). | |
| Reporting group title | Sub-study B: Tremelimumab |
| Reporting group description: Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by every 12 weeks (Q12W) for 24 weeks (up to 9 doses). | |

Primary: Overall Survival (OS)

| | |
|---|--------------------------------------|
| End point title | Overall Survival (OS) ^[1] |
| End point description: The OS was defined as the time from the date of randomization until death due to any cause. Sub-study A and B: Full analysis set (FAS) included all randomized participants analyzed on an intent-to-treat (ITT) basis. | |
| End point type | Primary |
| End point timeframe: From randomization (Day 1) until death due to any cause, approximately 36 months | |

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: no statistical analyses performed

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: SoC |
|----------------------------------|-------------------------|-------------------|--------------------------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: months | | | | |
| median (confidence interval 95%) | 11.7 (8.2 to 17.4) | 6.8 (4.9 to 10.2) | 11.5 (8.7 to 14.1) | 8.7 (6.5 to 11.7) |

Statistical analyses

| Statistical analysis title | Sub-study A: Durvalumab Vs SoC |
|---|--|
| Statistical analysis description: For sub-study A: durvalumab monotherapy treatment arm was compared with SoC. | |
| Comparison groups | Sub-study A: SoC v Sub-study A: Durvalumab |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.63 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.42 |
| upper limit | 0.93 |

Notes:

[2] - Sub-study A was not powered and thus no formal statistical comparisons were performed. Hazard ratio and confidence interval (CI) are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs SoC |
|---|---|
| Statistical analysis description: For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.109 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.05 |

Notes:

[3] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[4] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Primary: Progression-Free Survival (PFS)

| | |
|-----------------|--|
| End point title | Progression-Free Survival (PFS) ^[5] |
|-----------------|--|

End point description:

The PFS was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdrew from randomized therapy or received another anti-cancer therapy prior to progression. The PFS was determined by Investigator assessments according to response evaluation criteria in solid tumours (RECIST) version 1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 millimeter (mm) or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

Notes:

[5] - 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: no statistical analyses performed

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: SoC |
|----------------------------------|-------------------------|------------------|--------------------------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: months | | | | |
| median (confidence interval 95%) | 3.8 (1.9 to 5.6) | 2.2 (1.9 to 3.7) | 3.5 (2.3 to 4.6) | 3.5 (1.9 to 3.9) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs SoC |
|----------------------------|---|

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

| | |
|---|---|
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[6] |
| P-value | = 0.056 ^[7] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.59 |
| upper limit | 1.01 |

Notes:

[6] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[7] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

| | |
|---|--|
| Statistical analysis title | Sub-study A: Durvalumab Vs SoC |
| Statistical analysis description: For sub-study A: durvalumab monotherapy treatment arm was compared with SoC. | |
| Comparison groups | Sub-study A: Durvalumab v Sub-study A: SoC |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[8] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.04 |

Notes:

[8] - Sub-study A was not powered and thus no formal statistical comparisons were performed. Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

Secondary: OS, Contribution of the Components Analysis of Sub-study B

| | |
|--|---|
| End point title | OS, Contribution of the Components Analysis of Sub-study B ^[9] |
| End point description: The OS was defined as the time from the date of randomization until death due to any cause. The FAS included all randomized participants analyzed on an ITT basis. | |
| End point type | Secondary |
| End point timeframe: From randomization (Day 1) until death due to any cause, approximately 36 months | |

Notes:

[9] - 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: no statistical analyses performed

| End point values | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | |
|----------------------------------|--------------------------------------|-------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 174 | 117 | 60 | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.5 (8.7 to 14.1) | 10.0 (7.1 to 13.2) | 6.9 (3.9 to 13.2) | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab |
| Statistical analysis description: As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with durvalumab monotherapy. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: |

| | |
|---|-----------------------------|
| | Durvalumab |
| Number of subjects included in analysis | 291 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.885 ^[11] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.74 |
| upper limit | 1.3 |

Notes:

[10] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[11] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

| | |
|--|--|
| Statistical analysis title | Sub-study B: Durvalumab+TremelimumabVsTremelimumab |
| Statistical analysis description: | |
| As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | = 0.153 ^[13] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.78 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.11 |

Notes:

[12] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[13] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Secondary: Percentage of Participants Alive at 12 Months (OS12)

| | |
|--|--|
| End point title | Percentage of Participants Alive at 12 Months (OS12) |
| End point description: | |
| The OS12 was defined as the percentage of participants who were alive at 12 months after randomisation per Kaplan-Meier estimate of OS at 12 months. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization (Day 1) up to 12 months | |

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: SoC |
|-----------------------------------|-------------------------|---------------------|--------------------------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 49.3 (36.3 to 61.0) | 31.3 (20.2 to 43.0) | 49.5 (41.7 to 56.7) | 38.8 (29.9 to 47.7) |

| End point values | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | | |
|-----------------------------------|-------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 60 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 43.6 (34.4 to 52.4) | 41.2 (28.7 to 53.3) | | |

Statistical analyses

| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs SoC |
|---|---|
| Statistical analysis description: For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[14] |
| P-value | = 0.063 ^[15] |
| Method | z-test |

Notes:

[14] - The variance is estimated using the delta method and Greenwood's formula.

[15] - The z-test statistic is the ratio of log-transformed ratio of the cumulative hazards in the 2 treatment arms divided by square root of the variance.

Secondary: PFS, Contribution of the Components Analysis of Sub-study B

| | |
|-----------------|---|
| End point title | PFS, Contribution of the Components Analysis of Sub-study |
|-----------------|---|

End point description:

The PFS was defined as the time from the date of randomization until the date of objective disease progression or death (by any cause in the absence of progression) regardless of whether the participant withdrew from randomized therapy or received another anti-cancer therapy prior to progression. The PFS was determined by Investigator assessments according to RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. FAS included all randomized participants analyzed on an ITT basis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks

thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

Notes:

[16] - 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: no statistical analyses performed

| End point values | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | |
|----------------------------------|--------------------------------------|-------------------------|---------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 174 | 117 | 60 | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.5 (2.3 to 4.6) | 3.1 (1.9 to 3.7) | 2.1 (1.8 to 3.2) | |

Statistical analyses

| Statistical analysis title | Sub-study B: Durvalumab+TremelimumabVsTremelimumab |
|---|--|
| Statistical analysis description: As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.011 ^[18] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.67 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.92 |

Notes:

[17] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[18] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab |
|---|--|
| Statistical analysis description: As part of the contribution of components analysis for sub-study B, durvalumab plus tremelimumab treatment arm was compared with durvalumab monotherapy. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Durvalumab |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 291 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | = 0.282 ^[20] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.12 |

Notes:

[19] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[20] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Secondary: Objective Response Rate (ORR)

| | |
|-----------------|-------------------------------|
| End point title | Objective Response Rate (ORR) |
|-----------------|-------------------------------|

End point description:

The ORR was defined as the percentage of participants with at least 1 visit response of complete response (CR) or partial response (PR) among ITT participants who had measurable disease at baseline. CR was defined as disappearance of all target lesions (any pathological lymph nodes selected as target lesions must have a reduction in short axis to <10 mm) and PR was defined as at least a 30% decrease in the sum of diameters of target lesions (taking as reference the baseline sum of diameters as long as criteria for PD are not met). The ORR was measured using Investigator assessments according to RECIST v1.1. Sub-study A and B: FAS included all randomized participants with measureable disease at baseline analyzed on an ITT basis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: SoC |
|-----------------------------------|-------------------------|------------------|--------------------------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: percentage of participants | | | | |
| number (not applicable) | 35.5 | 12.5 | 14.9 | 6.8 |

| End point values | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | | |
|-----------------------------------|-------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 60 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 15.4 | 6.7 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Sub-study A: Durvalumab Vs SoC |
| Statistical analysis description: For sub-study A: durvalumab monotherapy treatment arm was compared with SoC. | |
| Comparison groups | Sub-study A: Durvalumab v Sub-study A: SoC |
| Number of subjects included in analysis | 126 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[21] |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 3.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.61 |
| upper limit | 10.1 |

Notes:

[21] - Sub-study A was not powered and thus no formal statistical comparisons were performed. The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

| | |
|--|--|
| Statistical analysis title | Sub-study B: Durvalumab+TremelimumabVsTremelimumab |
| Statistical analysis description: For sub-study B: durvalumab plus tremelimumab treatment arm was compared with tremelimumab monotherapy. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Tremelimumab |
| Number of subjects included in analysis | 234 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[22] |
| P-value | = 0.109 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.91 |
| upper limit | 8.61 |

Notes:

[22] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

| | |
|---|--|
| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs Durvalumab |
| Statistical analysis description: For sub-study B: durvalumab plus tremelimumab treatment arm was compared with durvalumab | |

monotherapy.

| | |
|---|--|
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: Durvalumab |
| Number of subjects included in analysis | 291 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | = 0.923 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.89 |

Notes:

[23] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

| | |
|---|---|
| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs SoC |
| Statistical analysis description: For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC. | |
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[24] |
| P-value | = 0.037 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 2.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.1 |
| upper limit | 5.94 |

Notes:

[24] - The analysis was performed using logistic regression adjusting for SoC therapy (gemcitabine/vinorelbine versus erlotinib) and histology (squamous versus all other histology types), with 95% CI calculated by profile likelihood.

Secondary: Duration of Response (DoR)

| | |
|---|----------------------------|
| End point title | Duration of Response (DoR) |
| End point description: The DoR was defined as the time from the date of first documented response until the first date of documented progression or death in the absence of disease progression. The DoR was determined by Investigator assessments according to RECIST v1.1. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants with measurable disease at baseline analyzed on an ITT basis. Only participants with objective response were analyzed. Here, '99999' denotes 'upper limit of 75th percentile was not reached'. | |
| End point type | Secondary |

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until confirmed disease progression. Assessed up to a maximum of approximately 3 years.

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+T remelimumab | Sub-study B: SoC |
|---------------------------------------|----------------------------|---------------------|---|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 22 | 8 | 26 | 8 |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 9.5 (3.0 to 17.8) | 4.8 (1.9 to 7.6) | 12.2 (6.5 to 99999) | 10.8 (5.6 to 12.2) |

| End point values | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | | |
|---------------------------------------|----------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 4 | | |
| Units: months | | | | |
| median (inter-quartile range (Q1-Q3)) | 10.0 (4.0 to 99999) | 4.7 (2.9 to 99999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive and Progression Free at 6 Months (APF6)

| | |
|-----------------|--|
| End point title | Percentage of Participants Alive and Progression Free at 6 Months (APF6) |
|-----------------|--|

End point description:

The APF6 was defined as the percentage of participants who were alive and progression free per RECIST v1.1 at 6 months after randomization per Kaplan-Meier estimate of PFS at 6 months. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 6 months

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+T remelimumab | Sub-study B: SoC |
|-----------------------------------|----------------------------|---------------------|---|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 35.5 (23.9 to 47.3) | 24.1 (14.1 to 35.6) | 31.5 (24.6 to 38.7) | 27.6 (19.0 to 36.7) |

| End point values | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | | |
|-----------------------------------|----------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 60 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27.2 (19.4 to 35.6) | 14.5 (6.9 to 24.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Alive and Progression Free at 12 Months (APF12)

| | |
|---|--|
| End point title | Percentage of Participants Alive and Progression Free at 12 Months (APF12) |
| End point description: | |
| The APF12 was defined as the percentage of participants who were alive and progression free per RECIST v1.1 at 12 months after randomization per Kaplan-Meier estimate of PFS at 12 months. PD was defined as at least a 20% increase in the sum of diameters of target lesions and an absolute increase of at least 5 mm or progression of non-target lesions or the appearance of a new lesion. Sub-study A and B: FAS included all randomized participants analyzed on an ITT basis. | |
| End point type | Secondary |
| End point timeframe: | |
| Tumour scans performed at baseline then every ~8 weeks up to 12 months. | |

| End point values | Sub-study A: Durvalumab | Sub-study A: SoC | Sub-study B: Durvalumab+T remelimumab | Sub-study B: SoC |
|-----------------------------------|----------------------------|---------------------|---|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 62 | 64 | 174 | 118 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 19.4 (10.7 to 30.0) | 9.9 (3.8 to 19.3) | 20.6 (14.7 to 27.1) | 8.0 (3.4 to 15.2) |

| End point values | Sub-study B: Durvalumab | Sub-study B: Tremelimumab | | |
|-----------------------------------|----------------------------|------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 60 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 15.0 (9.1 to 22.3) | 7.3 (2.4 to 16.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time From Randomisation to Second Progression (PFS2) of Sub-study B

| | |
|-----------------|---|
| End point title | Time From Randomisation to Second Progression (PFS2) of Sub-study B ^[25] |
|-----------------|---|

End point description:

The PFS2 was defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the PFS endpoint or death and determined by local standard clinical practice and have included any of the following: objective radiological, symptomatic progression, or death. PFS2 was reported for sub-study B only. The FAS included all randomized participants analyzed on an ITT basis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Tumour scans performed at baseline then every ~8 weeks up to 48 weeks, then every ~12 weeks thereafter until first progression. Disease then assessed per local practice until 2nd progression. Assessed up to a maximum of approximately 3 years.

Notes:

[25] - 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: no statistical analyses performed

| End point values | Sub-study B: Durvalumab+Tremelimumab | Sub-study B: SoC | Sub-study B: Durvalumab | Sub-study B: Tremelimumab |
|----------------------------------|--------------------------------------|------------------|-------------------------|---------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 174 | 118 | 117 | 60 |
| Units: months | | | | |
| median (confidence interval 95%) | 9.1 (6.6 to 12.3) | 6.7 (4.7 to 8.9) | 8.0 (6.3 to 10.0) | 5.7 (3.2 to 10.0) |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Sub-study B: Durvalumab+Tremelimumab Vs SoC |
|----------------------------|---|

Statistical analysis description:

For sub-study B: durvalumab plus tremelimumab treatment arm was compared with SoC.

| | |
|---|---|
| Comparison groups | Sub-study B: Durvalumab+Tremelimumab v Sub-study B: SoC |
| Number of subjects included in analysis | 292 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[26] |
| P-value | = 0.002 ^[27] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.85 |

Notes:

[26] - Hazard ratio and CI are estimated from a stratified Cox proportional hazards model with Breslow method to control for ties, stratification factors SoC therapy, and histology in strata statement, and CI is calculated using profile likelihood approach.

[27] - The P-value arises from a stratified log-rank test adjusting for SoC therapy and histology, with ties handled by the Breslow approach.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signature of informed consent up to 90 days after the last dose of durvalumab and/or tremelimumab and 30 days after the last dose of SoC, approximately 15 months.

Adverse event reporting additional description:

Sub-study A and B: Safety analysis set included all participants who received at least 1 dose of randomized treatment. Total # of deaths (all causes) was defined as death due to any cause (including disease progression) for the entire duration of the study assessed in all randomised participants.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------|
| Reporting group title | Sub-study A: SoC |
|-----------------------|------------------|

Reporting group description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m² IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Sub-study B: Durvalumab+Tremelimumab |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received durvalumab 20 mg/kg plus tremelimumab 1 mg/kg IV infusion Q4W for 12 weeks (4 doses) followed by durvalumab alone 10 mg/kg IV infusion Q2W for 34 weeks starting at Week 16 (up to 18 additional doses).

| | |
|-----------------------|-------------------------|
| Reporting group title | Sub-study A: Durvalumab |
|-----------------------|-------------------------|

Reporting group description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

| | |
|-----------------------|------------------|
| Reporting group title | Sub-study B: SoC |
|-----------------------|------------------|

Reporting group description:

Participants received either erlotinib 150 mg tablet orally once daily; gemcitabine 1000 mg/m² IV infusion on Days 1, 8, and 15 of a 28-day cycle; or vinorelbine 30 mg/m² IV infusion on Days 1, 8, 15, and 22 of a 28-day cycle until PD, initiation of alternative anticancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment criterion occurred.

| | |
|-----------------------|---------------------------|
| Reporting group title | Sub-study B: Tremelimumab |
|-----------------------|---------------------------|

Reporting group description:

Participants received tremelimumab 10 mg/kg IV infusion Q4W for 24 weeks followed by Q12W for 24 weeks (up to 9 doses).

| | |
|-----------------------|-------------------------|
| Reporting group title | Sub-study B: Durvalumab |
|-----------------------|-------------------------|

Reporting group description:

Participants received durvalumab 10 mg/kg IV infusion Q2W for 12 months (up to 26 doses).

| Serious adverse events | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study A: Durvalumab |
|---|------------------|--------------------------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 63 (25.40%) | 65 / 173 (37.57%) | 23 / 62 (37.10%) |
| number of deaths (all causes) | 55 | 118 | 48 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour necrosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer stage IV | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphangiosis carcinomatosa | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|-----------------|----------------|
| Internal haemorrhage | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Asthenia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perforation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 7 / 173 (4.05%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 2 / 173 (1.16%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 5 / 173 (2.89%) | 2 / 62 (3.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |

| | | | |
|---|----------------|-----------------|----------------|
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bronchial fistula | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 2 / 62 (3.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 3 / 62 (4.84%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 5 / 173 (2.89%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fractured ischium | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Vocal cord paralysis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 63 (3.17%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 3 / 173 (1.73%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 3 / 173 (1.73%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal toxicity | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 3 / 173 (1.73%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 3 / 173 (1.73%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic skin eruption | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucocorticoid deficiency | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inappropriate antidiuretic hormone | | | |

| | | | |
|---|----------------|-----------------|----------------|
| secretion | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thyroiditis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 2 / 173 (1.16%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|-----------------|----------------|
| Appendicitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis viral | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 7 / 173 (4.05%) | 4 / 62 (6.45%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 7 | 1 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 2 / 62 (3.23%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 1 / 62 (1.61%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 1 / 173 (0.58%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 63 (0.00%) | 0 / 173 (0.00%) | 0 / 62 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Sub-study B: SoC | Sub-study B: Tremelimumab | Sub-study B: Durvalumab |
|---|-------------------|---------------------------|-------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 28 / 110 (25.45%) | 23 / 60 (38.33%) | 36 / 117 (30.77%) |
| number of deaths (all causes) | 90 | 46 | 83 |
| number of deaths resulting from adverse events | 0 | 1 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Colorectal cancer | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour necrosis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer stage IV | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lymphangiosis carcinomatosa | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic venous thrombosis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Internal haemorrhage | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perforation | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden cardiac death | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| Immune system disorders | | | |
| Cytokine release syndrome | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | 0 / 60 (0.00%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumothorax spontaneous | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 1 / 60 (1.67%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|-----------------|----------------|-----------------|
| Bronchial fistula | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 2 / 60 (3.33%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 2 / 60 (3.33%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 1 / 1 |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| Mental status changes | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Overdose | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fractured ischium | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vocal cord paralysis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Brain oedema | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 7 / 60 (11.67%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 8 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Colitis | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 110 (0.00%) | 5 / 60 (8.33%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal toxicity | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subileus | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus paralytic | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Autoimmune hepatitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Drug-induced liver injury | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Toxic skin eruption | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| Urinary retention | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematuria | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glucocorticoid deficiency | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypopituitarism | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Thyroiditis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 2 / 60 (3.33%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Campylobacter gastroenteritis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|----------------|-----------------|
| Bronchitis viral | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Infection | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 2 / 110 (1.82%) | 2 / 60 (3.33%) | 2 / 117 (1.71%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Varicella zoster virus infection | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Sub-study A: SoC | Sub-study B: Durvalumab+Tremelimumab | Sub-study A: Durvalumab |
|---|------------------|--------------------------------------|-------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 59 / 63 (93.65%) | 139 / 173 (80.35%) | 52 / 62 (83.87%) |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 2 / 173 (1.16%) | 2 / 62 (3.23%) |
| occurrences (all) | 4 | 3 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 63 (3.17%) | 11 / 173 (6.36%) | 1 / 62 (1.61%) |
| occurrences (all) | 2 | 12 | 2 |
| Alanine aminotransferase increased | | | |

| | | | |
|--|------------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 3 / 63 (4.76%) 3 | 10 / 173 (5.78%) 11 | 1 / 62 (1.61%) 2 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 3 | 4 / 173 (2.31%) 4 | 4 / 62 (6.45%) 5 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 9 / 63 (14.29%) 33 | 2 / 173 (1.16%) 2 | 2 / 62 (3.23%) 2 |
| Platelet count decreased subjects affected / exposed occurrences (all) | 6 / 63 (9.52%) 8 | 1 / 173 (0.58%) 1 | 1 / 62 (1.61%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 14 / 173 (8.09%) 14 | 6 / 62 (9.68%) 7 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 6 / 63 (9.52%) 21 | 2 / 173 (1.16%) 2 | 1 / 62 (1.61%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 5 | 9 / 173 (5.20%) 10 | 6 / 62 (9.68%) 6 |
| Headache subjects affected / exposed occurrences (all) | 7 / 63 (11.11%) 8 | 17 / 173 (9.83%) 19 | 9 / 62 (14.52%) 11 |
| Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 8 | 2 / 173 (1.16%) 3 | 0 / 62 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 7 / 63 (11.11%) 40 | 3 / 173 (1.73%) 7 | 0 / 62 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 17 / 63 (26.98%) 22 | 17 / 173 (9.83%) 18 | 5 / 62 (8.06%) 5 |
| Thrombocytopenia | | | |

| | | | |
|---|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 10 | 3 / 173 (1.73%) 6 | 1 / 62 (1.61%) 2 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 8 / 63 (12.70%) | 31 / 173 (17.92%) | 6 / 62 (9.68%) |
| occurrences (all) | 17 | 39 | 6 |
| Fatigue | | | |
| subjects affected / exposed | 10 / 63 (15.87%) | 25 / 173 (14.45%) | 10 / 62 (16.13%) |
| occurrences (all) | 16 | 27 | 10 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 63 (9.52%) | 20 / 173 (11.56%) | 9 / 62 (14.52%) |
| occurrences (all) | 8 | 27 | 14 |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 16 / 173 (9.25%) | 6 / 62 (9.68%) |
| occurrences (all) | 5 | 17 | 8 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 63 (3.17%) | 4 / 173 (2.31%) | 4 / 62 (6.45%) |
| occurrences (all) | 3 | 4 | 4 |
| Malaise | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 3 / 173 (1.73%) | 1 / 62 (1.61%) |
| occurrences (all) | 8 | 3 | 1 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 8 / 63 (12.70%) | 36 / 173 (20.81%) | 9 / 62 (14.52%) |
| occurrences (all) | 8 | 45 | 13 |
| Nausea | | | |
| subjects affected / exposed | 15 / 63 (23.81%) | 28 / 173 (16.18%) | 11 / 62 (17.74%) |
| occurrences (all) | 20 | 33 | 12 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 63 (7.94%) | 10 / 173 (5.78%) | 5 / 62 (8.06%) |
| occurrences (all) | 5 | 11 | 6 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 63 (6.35%) | 17 / 173 (9.83%) | 8 / 62 (12.90%) |
| occurrences (all) | 5 | 17 | 8 |
| Abdominal pain | | | |

| | | | |
|---|------------------------|-------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 5 / 173 (2.89%) 5 | 4 / 62 (6.45%) 4 |
| Constipation subjects affected / exposed occurrences (all) | 15 / 63 (23.81%) 16 | 14 / 173 (8.09%) 15 | 13 / 62 (20.97%) 15 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 2 / 173 (1.16%) 2 | 1 / 62 (1.61%) 1 |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) | 9 / 63 (14.29%) 11 | 25 / 173 (14.45%) 26 | 11 / 62 (17.74%) 12 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 4 / 173 (2.31%) 4 | 6 / 62 (9.68%) 6 |
| Haemoptysis subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 6 / 173 (3.47%) 7 | 4 / 62 (6.45%) 8 |
| Cough subjects affected / exposed occurrences (all) | 5 / 63 (7.94%) 5 | 24 / 173 (13.87%) 29 | 11 / 62 (17.74%) 13 |
| Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 4 / 173 (2.31%) 4 | 0 / 62 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 9 / 63 (14.29%) 9 | 14 / 173 (8.09%) 15 | 3 / 62 (4.84%) 4 |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 28 / 173 (16.18%) 36 | 7 / 62 (11.29%) 8 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 6 / 63 (9.52%) 6 | 6 / 173 (3.47%) 11 | 3 / 62 (4.84%) 4 |
| Psychiatric disorders | | | |

| | | | |
|--|---------------------|------------------------|----------------------|
| Insomnia subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 6 / 173 (3.47%) 6 | 7 / 62 (11.29%) 7 |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | 14 / 173 (8.09%) 15 | 6 / 62 (9.68%) 6 |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 17 / 173 (9.83%) 17 | 2 / 62 (3.23%) 2 |
| Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 9 / 173 (5.20%) 11 | 2 / 62 (3.23%) 2 |
| Myalgia subjects affected / exposed occurrences (all) | 3 / 63 (4.76%) 4 | 9 / 173 (5.20%) 9 | 2 / 62 (3.23%) 2 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 4 / 63 (6.35%) 4 | 7 / 173 (4.05%) 10 | 6 / 62 (9.68%) 8 |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 2 / 63 (3.17%) 2 | 7 / 173 (4.05%) 7 | 3 / 62 (4.84%) 5 |
| Back pain subjects affected / exposed occurrences (all) | 6 / 63 (9.52%) 7 | 11 / 173 (6.36%) 13 | 7 / 62 (11.29%) 7 |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 63 (4.76%) 3 | 16 / 173 (9.25%) 19 | 7 / 62 (11.29%) 8 |
| Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 63 (1.59%) 1 | 15 / 173 (8.67%) 18 | 3 / 62 (4.84%) 5 |
| Influenza subjects affected / exposed occurrences (all) | 0 / 63 (0.00%) 0 | 3 / 173 (1.73%) 3 | 2 / 62 (3.23%) 3 |

| | | | |
|------------------------------------|------------------|-------------------|------------------|
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 63 (4.76%) | 3 / 173 (1.73%) | 5 / 62 (8.06%) |
| occurrences (all) | 3 | 3 | 6 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 0 / 173 (0.00%) | 5 / 62 (8.06%) |
| occurrences (all) | 2 | 0 | 5 |
| Decreased appetite | | | |
| subjects affected / exposed | 20 / 63 (31.75%) | 34 / 173 (19.65%) | 16 / 62 (25.81%) |
| occurrences (all) | 24 | 39 | 19 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 63 (1.59%) | 1 / 173 (0.58%) | 1 / 62 (1.61%) |
| occurrences (all) | 3 | 1 | 1 |

| Non-serious adverse events | Sub-study B: SoC | Sub-study B: Tremelimumab | Sub-study B: Durvalumab |
|---|--------------------|---------------------------|-------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 100 / 110 (90.91%) | 48 / 60 (80.00%) | 99 / 117 (84.62%) |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 110 (2.73%) | 2 / 60 (3.33%) | 4 / 117 (3.42%) |
| occurrences (all) | 6 | 2 | 5 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 8 / 110 (7.27%) | 5 / 60 (8.33%) | 2 / 117 (1.71%) |
| occurrences (all) | 12 | 6 | 5 |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 10 / 110 (9.09%) | 5 / 60 (8.33%) | 5 / 117 (4.27%) |
| occurrences (all) | 15 | 6 | 9 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 1 / 60 (1.67%) | 1 / 117 (0.85%) |
| occurrences (all) | 1 | 1 | 2 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 18 / 110 (16.36%) | 0 / 60 (0.00%) | 1 / 117 (0.85%) |
| occurrences (all) | 43 | 0 | 1 |
| Platelet count decreased | | | |
| subjects affected / exposed | 8 / 110 (7.27%) | 0 / 60 (0.00%) | 0 / 117 (0.00%) |
| occurrences (all) | 27 | 0 | 0 |

| | | | |
|--|-------------------------|----------------------|-------------------------|
| Weight decreased subjects affected / exposed occurrences (all) | 4 / 110 (3.64%) 4 | 4 / 60 (6.67%) 4 | 8 / 117 (6.84%) 8 |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 11 / 110 (10.00%) 32 | 0 / 60 (0.00%) 0 | 1 / 117 (0.85%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 6 | 3 / 60 (5.00%) 3 | 8 / 117 (6.84%) 8 |
| Headache subjects affected / exposed occurrences (all) | 6 / 110 (5.45%) 8 | 5 / 60 (8.33%) 6 | 8 / 117 (6.84%) 8 |
| Blood and lymphatic system disorders | | | |
| Leukopenia subjects affected / exposed occurrences (all) | 7 / 110 (6.36%) 15 | 1 / 60 (1.67%) 1 | 0 / 117 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 18 / 110 (16.36%) 48 | 1 / 60 (1.67%) 3 | 0 / 117 (0.00%) 0 |
| Anaemia subjects affected / exposed occurrences (all) | 27 / 110 (24.55%) 49 | 5 / 60 (8.33%) 5 | 11 / 117 (9.40%) 13 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 11 / 110 (10.00%) 15 | 2 / 60 (3.33%) 2 | 4 / 117 (3.42%) 4 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 17 / 110 (15.45%) 19 | 9 / 60 (15.00%) 9 | 16 / 117 (13.68%) 21 |
| Fatigue subjects affected / exposed occurrences (all) | 24 / 110 (21.82%) 30 | 4 / 60 (6.67%) 4 | 22 / 117 (18.80%) 24 |
| Pyrexia subjects affected / exposed occurrences (all) | 23 / 110 (20.91%) 33 | 6 / 60 (10.00%) 7 | 12 / 117 (10.26%) 15 |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| Oedema peripheral subjects affected / exposed occurrences (all) | 9 / 110 (8.18%) 10 | 2 / 60 (3.33%) 3 | 8 / 117 (6.84%) 10 |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 4 / 110 (3.64%) 4 | 1 / 60 (1.67%) 1 | 2 / 117 (1.71%) 2 |
| Malaise subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 5 | 1 / 60 (1.67%) 1 | 8 / 117 (6.84%) 8 |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 18 / 110 (16.36%) 26 | 16 / 60 (26.67%) 20 | 25 / 117 (21.37%) 33 |
| Nausea subjects affected / exposed occurrences (all) | 22 / 110 (20.00%) 32 | 11 / 60 (18.33%) 16 | 20 / 117 (17.09%) 25 |
| Stomatitis subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 6 | 1 / 60 (1.67%) 3 | 3 / 117 (2.56%) 3 |
| Vomiting subjects affected / exposed occurrences (all) | 8 / 110 (7.27%) 13 | 7 / 60 (11.67%) 10 | 18 / 117 (15.38%) 22 |
| Abdominal pain subjects affected / exposed occurrences (all) | 2 / 110 (1.82%) 5 | 2 / 60 (3.33%) 2 | 2 / 117 (1.71%) 2 |
| Constipation subjects affected / exposed occurrences (all) | 11 / 110 (10.00%) 12 | 4 / 60 (6.67%) 4 | 15 / 117 (12.82%) 16 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 4 / 110 (3.64%) 6 | 2 / 60 (3.33%) 2 | 7 / 117 (5.98%) 7 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 15 / 110 (13.64%) 16 | 6 / 60 (10.00%) 6 | 16 / 117 (13.68%) 17 |
| Rhinorrhoea | | | |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 2 / 110 (1.82%) 2 | 1 / 60 (1.67%) 1 | 1 / 117 (0.85%) 1 |
| Haemoptysis subjects affected / exposed occurrences (all) | 4 / 110 (3.64%) 4 | 1 / 60 (1.67%) 1 | 7 / 117 (5.98%) 7 |
| Cough subjects affected / exposed occurrences (all) | 14 / 110 (12.73%) 15 | 5 / 60 (8.33%) 5 | 15 / 117 (12.82%) 20 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 5 | 3 / 60 (5.00%) 3 | 4 / 117 (3.42%) 6 |
| Rash subjects affected / exposed occurrences (all) | 17 / 110 (15.45%) 17 | 9 / 60 (15.00%) 11 | 7 / 117 (5.98%) 9 |
| Pruritus subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 5 | 14 / 60 (23.33%) 17 | 11 / 117 (9.40%) 12 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 4 / 110 (3.64%) 4 | 0 / 60 (0.00%) 0 | 1 / 117 (0.85%) 1 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 5 | 5 / 60 (8.33%) 5 | 7 / 117 (5.98%) 7 |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 1 / 110 (0.91%) 1 | 3 / 60 (5.00%) 4 | 10 / 117 (8.55%) 11 |
| Hyperthyroidism subjects affected / exposed occurrences (all) | 0 / 110 (0.00%) 0 | 1 / 60 (1.67%) 1 | 6 / 117 (5.13%) 7 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 110 (4.55%) 5 | 6 / 60 (10.00%) 7 | 9 / 117 (7.69%) 11 |

| | | | |
|---|-------------------|------------------|-------------------|
| Myalgia | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | 1 / 60 (1.67%) | 5 / 117 (4.27%) |
| occurrences (all) | 4 | 1 | 5 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | 1 / 60 (1.67%) | 12 / 117 (10.26%) |
| occurrences (all) | 5 | 1 | 12 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | 2 / 60 (3.33%) | 7 / 117 (5.98%) |
| occurrences (all) | 2 | 2 | 7 |
| Back pain | | | |
| subjects affected / exposed | 4 / 110 (3.64%) | 4 / 60 (6.67%) | 14 / 117 (11.97%) |
| occurrences (all) | 4 | 4 | 15 |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | 4 / 60 (6.67%) | 10 / 117 (8.55%) |
| occurrences (all) | 4 | 5 | 10 |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 110 (4.55%) | 1 / 60 (1.67%) | 7 / 117 (5.98%) |
| occurrences (all) | 5 | 1 | 8 |
| Influenza | | | |
| subjects affected / exposed | 0 / 110 (0.00%) | 1 / 60 (1.67%) | 6 / 117 (5.13%) |
| occurrences (all) | 0 | 1 | 6 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 110 (1.82%) | 9 / 60 (15.00%) | 8 / 117 (6.84%) |
| occurrences (all) | 2 | 10 | 10 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 0 / 60 (0.00%) | 4 / 117 (3.42%) |
| occurrences (all) | 1 | 0 | 5 |
| Decreased appetite | | | |
| subjects affected / exposed | 23 / 110 (20.91%) | 12 / 60 (20.00%) | 27 / 117 (23.08%) |
| occurrences (all) | 24 | 12 | 28 |
| Dehydration | | | |
| subjects affected / exposed | 1 / 110 (0.91%) | 4 / 60 (6.67%) | 0 / 117 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 18 June 2014 | Key changes from this amendment are listed under Amendment 3. |
| 28 July 2014 | Key changes from this amendment are listed under Amendment 3. |
| 08 October 2014 | The study design was updated to include 2 independent sub-studies as follows: Sub-study A was designed to enroll PD-L1 high non-small cell lung cancer (NSCLC) participants into either the durvalumab monotherapy arm or SoC treatment arm in a 1:1 ratio. Sub-study B was designed to enroll PD-L1 low/neg NSCLC participants into either durvalumab in combination with tremelimumab treatment arm, durvalumab monotherapy arm, tremelimumab monotherapy arm, or SoC treatment arm in a 1:1:1:1 ratio. PD-L1 tumor status was assessed as part of the pre-screening process. The study objectives were updated to include the additional treatment arms. Participants selection criteria were updated to include new treatment arms, PD-L1 tumor status (including requirements for archival tumor sample), retreatment criteria, additional exclusion criteria for sub-study B, and restrictions during the study. Descriptions of study treatments, treatment regimens, management of toxicity and adverse event of special interest (AESI), treatment compliance, and discontinuation of study treatment were updated. The evaluation and calculation of study variables, and statistical methods were updated. |
| 27 March 2015 | Deep sustained response was removed from the secondary objectives and endpoints. The dose regimen for sub-study B durvalumab in combination with tremelimumab treatment arm was updated to durvalumab 20 mg/kg plus tremelimumab 1 mg/kg Q4W IV for up to 12 weeks (4 doses) then durvalumab alone (10 mg/kg Q2W IV, starting at Week 16, for 34 weeks [18 doses]). Randomization to treatment arms for sub-study B was changed to a 3:2:2:1 ratio (durvalumab in combination with tremelimumab: SoC: durvalumab monotherapy: tremelimumab monotherapy, respectively). Language was updated to allow participants enrolled in the durvalumab in combination with tremelimumab treatment arm of sub-study B who progress while in the durvalumab monotherapy period to be retreated with the combination. Clarification of the process of treatment and retreatment in each sub-study was also provided. The exclusion criterion regarding participants with known epidermal growth factor receptor (EGFR) tyrosine kinase (TK) activating mutations was updated to allow participants with EGFR TK inactivating mutations (eg, exon 20) to enroll. |
| 30 December 2015 | Language regarding treatment through disease progression and retreatment within the inclusion criteria was updated and moved to a separate section of the protocol. New safety data were added, including an updated list of AESIs and a new appendix containing dose modification and toxicity management guidelines. Inclusion criteria 6 and 7 were updated with new parameters for both mandatory and optional archival tumor samples. Exclusion criterion 2 was updated to exclude participants from other durvalumab studies, and the language regarding participants with tuberculosis in exclusion criterion 25 was updated. |

| | |
|-------------------|--|
| 31 August 2016 | The number of participants planned, determination of sample size, and statistics were updated. The outcome measures using blinded independent central review (BICR) assessments according to RECIST v1.1 were removed and replaced with Investigator assessments according to RECIST v1.1. The exploratory objective and outcome utilizing BICR assessments according to immune-related response criteria were also removed. Language was updated to clarify that the interim analysis will be conducted for Sub-study B only. The retreatment exclusion criteria were updated to remove the 28-day wash-out period before retreatment. The text regarding immunosuppressive medication was updated, and 3 additional criteria for concomitant medication use were included. |
| 19 September 2017 | The maximum period of retreatment was updated for all immunotherapy arms from a maximum of 12 months to as long as the participant gained clinical benefit, as judged by the Investigator. The dose modification and toxicity management guidelines for immune-mediated, infusion-related, and non immune-mediated reactions were updated, and language was updated on AESIs, including the list of AESIs. Language was added regarding timing of final PFS and OS analyses. |
| 08 January 2018 | The toxicity management guidelines for immune-mediated, infusion-related, and non-immune-mediated reactions and list of AESIs were updated. |
| 07 February 2020 | Toxicity management guidelines will be a separate annex to the protocol. Administrative changes. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported