



Clinical trial results:

An Open-Label, Multi-Center, Safety Study of Fixed-Dose Durvalumab + Tremelimumab Combination Therapy or Durvalumab Monotherapy in Advanced Solid Malignancies (STRONG) Module A – Post-Chemotherapy Urothelial and NonUrothelial Carcinoma of the Urinary Tract with Fixed-dose Durvalumab

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2016-005068-33 |
| Trial protocol | DE GB FR IT |
| Global end of trial date | 16 December 2022 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 28 October 2023 |
| First version publication date | 28 October 2023 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | D4191C00068 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03084471 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AstraZeneca Clinical study Information Center |
| Sponsor organisation address | Södertälje, Södertälje, Sweden, 151 85 |
| Public contact | AstraZeneca Clinical study Information Center, AstraZeneca Clinical study Information Center, +1 8772409479, information.center@astrazeneca.com |
| Scientific contact | Global Clinical Lead, AstraZeneca Clinical study Information Center, +1 8772409479, information.center@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 July 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 December 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality, including immune-relatedness, of adverse events (AEs) of special interest (AESIs) in patients with locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract (including the urinary bladder, ureter, urethra and renal pelvis) who were treated with a fixed-dose of durvalumab monotherapy.

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 the International Conference on Harmonisation/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics and Human Biological Samples. Before enrollment of any patient into the study, the final protocol, including the final version of the informed consent form, was approved by the national regulatory authority or a notification to the national regulatory authority was done, according to local regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 17 April 2017 |
| 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 | Canada: 55 |
| Country: Number of subjects enrolled | France: 468 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Italy: 210 |
| Country: Number of subjects enrolled | Korea, Republic of: 61 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects | 867 |
| EEA total number of subjects | 717 |

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) | 326 |
| From 65 to 84 years | 528 |
| 85 years and over | 13 |

Subject disposition

Recruitment

Recruitment details:

Patients who met all the inclusion and none of the exclusion criteria were randomized at 77 study centers across 8 countries (Canada, France, Germany, Italy, Republic of Korea, Netherlands, United Kingdom and United States of America).

Pre-assignment

Screening details:

During the screening period (4 weeks), eligible patients signed the informed consent. All the study assessments were performed as per the schedule of assessment.

Period 1

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

Arms

| | |
|-----------|------------|
| Arm title | Durvalumab |
|-----------|------------|

Arm description:

All patients received fixed-dose of durvalumab 1500 mg every 4 weeks until disease progression or unacceptable toxicity.

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

Dosage and administration details:

Patients received 1500 mg durvalumab via intravenous (IV) infusion every 4 weeks (Q4W) until confirmed disease progression unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

| Number of subjects in period 1 | Durvalumab |
|---|------------|
| Started | 867 |
| Completed | 0 |
| Not completed | 867 |
| Study specific discontinuation criteria | 2 |
| Consent withdrawn by subject | 12 |
| Other (as recorded) | 33 |
| Lack of therapeutic response | 2 |
| Adverse event, non-fatal | 73 |
| Condition under investigation worsened | 84 |
| Disease relapse | 181 |
| Subjective disease progression | 359 |

| | |
|----------------------------------|-----|
| Ongoing patients at data cut-off | 120 |
| Protocol deviation | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Durvalumab |
|-----------------------|------------|

Reporting group description:

All patients received fixed-dose of durvalumab 1500 mg every 4 weeks until disease progression or unacceptable toxicity.

| Reporting group values | Durvalumab | Total | |
|--|------------|-------|--|
| Number of subjects | 867 | 867 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 326 | 326 | |
| From 65-84 years | 528 | 528 | |
| 85 years and over | 13 | 13 | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 67.5 | | |
| standard deviation | ± 9.36 | - | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 173 | 173 | |
| Male | 694 | 694 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 65 | 65 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 2 | 2 | |
| White | 508 | 508 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 264 | 264 | |
| Other | 28 | 28 | |

End points

End points reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Durvalumab |
|-----------------------|------------|

Reporting group description:

All patients received fixed-dose of durvalumab 1500 mg every 4 weeks until disease progression or unacceptable toxicity.

| | |
|----------------------------|--|
| Subject analysis set title | Adverse events of special interest (AESIs) |
|----------------------------|--|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

AESIs are defined as AEs with a likely inflammatory or immune-mediated pathophysiological basis, resulting from the mechanism of action of durvalumab and/or tremelimumab and requiring more frequent monitoring and/or interventions, such as corticosteroids, immunosuppressants, and/or endocrine therapy.

| | |
|----------------------------|---|
| Subject analysis set title | Adverse events of possible interest (AEPIs) |
|----------------------------|---|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

AEPIs are defined as AEs that could have a potential inflammatory or immune-mediated pathophysiological basis, resulting from the mechanism of action of durvalumab but are more likely to have occurred due to other pathophysiological mechanisms, thus, the likelihood of the event being inflammatory or immune-mediated in nature is not high and/or is most often or usually explained by the other causes.

| | |
|----------------------------|--|
| Subject analysis set title | Immune-mediated adverse events (imAEs) |
|----------------------------|--|

| | |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

The imAEs that occurred during this study were determined by a programmatic algorithm that required specific treatment for AESIs to be considered imAEs; the same specific treatment was required for AEPIs as well.

Primary: Number of patients with adverse events of special interest (AESIs), adverse events of possible interest (AEPIs) and immune-mediated adverse events (imAEs)

| | |
|-----------------|---|
| End point title | Number of patients with adverse events of special interest (AESIs), adverse events of possible interest (AEPIs) and immune-mediated adverse events (imAEs) ^[1] |
|-----------------|---|

End point description:

Incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of adverse events of special interest (AESIs) were assessed. AESIs included events with a potential inflammatory or immune-mediated mechanism that required interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. Serious adverse event (SAE); Common Terminology Criteria for Adverse Events (CTCAE); Investigational product (IP). Safety analysis set: all enrolled participants who received at least one dose of durvalumab.

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

End point timeframe:

From screening to safety follow up visit (90 days after last dose), up to approximately 3 years.

Notes:

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

Justification: No statistical analysis was performed

| End point values | Adverse events of special interest (AESIs) | Adverse events of possible interest (AEPis) | Immune-mediated adverse events (imAEs) | |
|---|--|---|--|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 867 | 867 | 867 | |
| Units: Patients | | | | |
| Any adverse event (AE) | 265 | 300 | 97 | |
| Any AE of CTCAE Grade 3 or 4 | 21 | 49 | 17 | |
| Any SAE (events outcome = death) | 19 | 13 | 11 | |
| Any AE with outcome = death | 1 | 0 | 0 | |
| Any AE, related to IP | 191 | 145 | 87 | |
| Any AE of CTCAE Grade 3 or 4, related to IP | 15 | 20 | 16 | |
| Any SAE, related to treatment | 14 | 3 | 10 | |
| Any AE with outcome = death, related to IP | 1 | 0 | 0 | |
| Any AE leading to discontinuation of IP | 12 | 7 | 10 | |
| Event outcome resolved | 140 | 119 | 32 | |
| Event outcome not resolved | 124 | 181 | 65 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival was defined as the time from the first date of treatment until death due to any cause.
Safety analysis set: all enrolled participants who received at least 1 dose of durvalumab.

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

End point timeframe:

From screening to final data cutoff (maximum up to 4 years) following date of first patient treatment initiation.

| End point values | Durvalumab | | | |
|----------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 867 | | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.0 (6.44 to 8.18) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with adverse events

| | |
|-----------------|--|
| End point title | Number of patients with adverse events |
|-----------------|--|

End point description:

Incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of treatment-emergent AEs (including SAEs) was assessed. Safety analysis set: all enrolled participants who received at least one dose of durvalumab.

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

End point timeframe:

From screening to safety follow up visit (90 days after last dose), maximum up to 4 years.

| End point values | Durvalumab | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 867 | | | |
| Units: Patients | | | | |
| Any AE | 787 | | | |
| Any AE related to IP | 407 | | | |
| Any AE of CTCAE grade 3 or higher | 365 | | | |
| Any AE of CTCAE grade 3 or higher, related to IP | 78 | | | |
| Any AE with outcome = death | 42 | | | |
| Any AE with outcome = death related to IP | 9 | | | |
| Any SAE (including events with outcome = death) | 254 | | | |
| Any SAE (events outcome = death) related to IP | 41 | | | |
| Any AE leading to discontinuation of IP | 77 | | | |
| IP-related AE leading to discontinuation | 33 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From screening to safety follow up visit (90 days after last dose), maximum up to 4 years.

Adverse event reporting additional description:

MedDRA version 23.0

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Durvalumab |
|-----------------------|------------|

Reporting group description:

All participants received fixed-dose of durvalumab 1500 mg every 4 weeks until disease progression or unacceptable toxicity.

| Serious adverse events | Durvalumab | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 254 / 867 (29.30%) | | |
| number of deaths (all causes) | 600 | | |
| number of deaths resulting from adverse events | 43 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour hyperprogression | | | |
| subjects affected / exposed | 11 / 867 (1.27%) | | |
| occurrences causally related to treatment / all | 10 / 11 | | |
| deaths causally related to treatment / all | 7 / 8 | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bladder cancer recurrent | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bladder neoplasm | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchial carcinoma | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cancer pain | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastric cancer | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected neoplasm | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lymphangiosis carcinomatosa | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuroendocrine tumour | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pelvic neoplasm | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal cancer | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tumour pain | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 7 / 867 (0.81%) | | |
| occurrences causally related to treatment / all | 1 / 7 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Death | | | |
| subjects affected / exposed | 5 / 867 (0.58%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug intolerance | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthermia malignant | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular stent thrombosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Haemophagocytic lymphohistiocytosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Scrotal mass | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 7 / 867 (0.81%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung disorder | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchiectasis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Interstitial lung disease | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural thickening | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Confusional state | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Delirium | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|-----------------|--|--|
| Mental status changes | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stent malfunction | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 5 / 867 (0.58%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Troponin increased | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Postoperative ileus | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Stomal hernia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Urinary tract stoma complication | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Coronary artery occlusion | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Basilar artery occlusion | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolic stroke | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Frontal lobe epilepsy | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| IIIrd nerve paralysis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peroneal nerve palsy | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Somnolence | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VIth nerve disorder | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 867 (0.69%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 867 (0.81%) | | |
| occurrences causally related to treatment / all | 1 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal pain | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 5 / 867 (0.58%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subileus | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anal fistula | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Autoimmune colitis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis ischaemic | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Duodenal ulcer | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Duodenitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterovesical fistula | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus paralytic | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intestinal atony | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Intestinal pseudo-obstruction | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 5 / 867 (0.58%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 7 / 867 (0.81%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 8 / 867 (0.92%) | | |
| occurrences causally related to treatment / all | 2 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urine abnormality | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 867 (0.46%) | | |
| occurrences causally related to treatment / all | 2 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract inflammation | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ureteric stenosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophysitis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Pain in extremity | | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Back pain | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Musculoskeletal chest pain | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arthralgia | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flank pain | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lumbar spinal stenosis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Muscular weakness | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neck pain | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Rotator cuff syndrome | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 7 / 867 (0.81%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 8 / 867 (0.92%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 17 / 867 (1.96%) | | |
| occurrences causally related to treatment / all | 0 / 21 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 18 / 867 (2.08%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Urosepsis | | | |
| subjects affected / exposed | 5 / 867 (0.58%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 867 (0.69%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| COVID-19 | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Clostridium colitis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diverticulitis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterobacter infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterobacter sepsis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Escherichia urinary tract infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fournier's gangrene | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatitis E | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumocystis jirovecii infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Staphylococcal infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Staphylococcal sepsis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Streptococcal infection | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacteraemia | | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atypical pneumonia | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cellulitis | | | | |
| subjects affected / exposed | 2 / 867 (0.23%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bacterial infection | | | | |
| subjects affected / exposed | 3 / 867 (0.35%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis acute | | | | |
| subjects affected / exposed | 4 / 867 (0.46%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tracheitis | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection enterococcal | | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ketoacidosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 867 (0.12%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Durvalumab | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 669 / 867 (77.16%) | | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 48 / 867 (5.54%) | | |
| occurrences (all) | 54 | | |
| Weight decreased | | | |
| subjects affected / exposed | 46 / 867 (5.31%) | | |
| occurrences (all) | 48 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 228 / 867 (26.30%) | | |
| occurrences (all) | 250 | | |
| Pyrexia | | | |
| subjects affected / exposed | 79 / 867 (9.11%) | | |
| occurrences (all) | 92 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 75 / 867 (8.65%) | | |
| occurrences (all) | 79 | | |
| Fatigue | | | |
| subjects affected / exposed | 83 / 867 (9.57%) | | |
| occurrences (all) | 96 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 172 / 867 (19.84%) | | |
| occurrences (all) | 186 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 171 / 867 (19.72%) | | |
| occurrences (all) | 190 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 136 / 867 (15.69%) | | |
| occurrences (all) | 173 | | |
| Nausea | | | |
| subjects affected / exposed | 126 / 867 (14.53%) | | |
| occurrences (all) | 141 | | |
| Vomiting | | | |
| subjects affected / exposed | 76 / 867 (8.77%) | | |
| occurrences (all) | 86 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 64 / 867 (7.38%) | | |
| occurrences (all) | 73 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 84 / 867 (9.69%) | | |
| occurrences (all) | 91 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 74 / 867 (8.54%) | | |
| occurrences (all) | 81 | | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 109 / 867 (12.57%) | | |
| occurrences (all) | 142 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 64 / 867 (7.38%) | | |
| occurrences (all) | 77 | | |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 57 / 867 (6.57%) | | |
| occurrences (all) | 64 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>82 / 867 (9.46%)</p> <p>84</p> <p>65 / 867 (7.50%)</p> <p>75</p> | | |
| <p>Infections and infestations</p> <p>Urinary tract infection</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>84 / 867 (9.69%)</p> <p>95</p> | | |
| <p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>149 / 867 (17.19%)</p> <p>156</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 01 March 2017 | Version 2: AEs that met criteria for IP discontinuation were updated following updated Toxicity Management Guidelines. |
| 19 April 2017 | Version 3: Screening and other assessments were updated to align with new durvalumab+/-tremelimumab protocol template. This includes clarification /corrections of urinalysis, vital signs, and weight/height. Exclusion criteria were updated to include patients who had adequate organ or marrow function irrespective of dependence on transfusion or growth factor support. An option to collect tumor tissue was added in case an archival sample was not available and patient consented to sample collection. |
| 08 February 2018 | Version 4: Inclusion and exclusion criteria were updated to align with the new durvalumab+/-tremelimumab protocol template. Additional inflammatory responses were added to AESIs to align with the updated Investigator's brochure. Removal of redundant procedure (height was not needed at baseline as well as screening). |
| 13 December 2019 | Version 5: Safety (AESIs) and risks were updated to align with durvalumab IB and tremelimumab IB. The protocol deviation related to infusion time < 55 minutes was removed to align with the durvalumab+/-tremelimumab protocol template. Overall study duration (clarified as 4 to 5 years), dates/duration for survival follow-up, deletion of specific instructions for immune-mediated adverse event (imAE) follow-up, clarification of SAE reporting and collection of safety data for patients who continued receiving treatment once the final data cut-off (DCO) is reached, and duration of treatment and criteria for treatment through progression and for retreatment. Exclusion criterion 4 was corrected to state that participation in another clinical study with an IP during the last 28 days or 5 half-lives, whichever is longer, prior to the first dose of study treatment. New malignant tumors were added as a category of SAEs. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported