



Clinical trial results:

Phase III study comparing maintenance by pemetrexed or gemcitabine to surveillance in elderly patient (70 year old) with advanced Non Small Cell Lung Cancer controlled by induction chemotherapy

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2012-005520-15 |
| Trial protocol | FR |
| Global end of trial date | 31 January 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 26 January 2023 |
| First version publication date | 26 January 2023 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | IFCT-1201 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01850303 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | IFCT |
| Sponsor organisation address | 10 Rue de la Grange Batelière , Paris, France, 75009 |
| Public contact | Contact, IFCT, 33 1.56.81.10.46, contact@ifct.fr |
| Scientific contact | Contact, IFCT, 33 1.56.81.10.46, contact@ifct.fr |

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 | 01 July 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-----------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 31 January 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Overall survival of patients whose disease is controlled after induction chemotherapy with 4 cycles of carboplatin and paclitaxel weekly from randomization maintenance versus observation.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2013 |
| 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 | France: 627 |
| Worldwide total number of subjects | 627 |
| EEA total number of subjects | 627 |

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) | 0 |
| From 65 to 84 years | 601 |
| 85 years and over | 26 |

Subject disposition

Recruitment

Recruitment details:

632 patients were enrolled from May 2013 to October 2016. Of the 328 (52.3%) patients randomised after induction therapy, 166 patients were assigned to the observation arm, versus 162 to the switch maintenance arm, 119 of whom received pemetrexed and 43 gemcitabine.

Pre-assignment

Screening details:

Patients should have a histologically/cytologically confirmed stage IV or III not amenable to surgery or radiotherapy NSCLC, an age between 70 and 89 years, a performance status (PS) 0-2, a mini-mental score (MMS) > 23/30 and appropriate hepatic and renal functions and haematopoietic reserves.

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Induction |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|---------------------------------------|
| Arm title | Paclitaxel - Carboplatin |
| Arm description: - | |
| Arm type | Induction |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Paclitaxel IV 90 mg/m² at D1, D8, D15 ; cycles repeated every 28 days.

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

Dosage and administration details:

Carboplatin IV AUC6 (D1= D29); cycles repeated every 28 days.

| Number of subjects in period 1 | Paclitaxel - Carboplatin |
|--------------------------------|--------------------------|
| Started | 627 |
| Completed | 328 |
| Not completed | 299 |
| Consent withdrawn by subject | 19 |
| Physician decision | 2 |
| Adverse event, non-fatal | 39 |
| Death | 53 |

| | |
|------------------------|-----|
| Not specified | 11 |
| Performans status >2 | 12 |
| Treatment not received | 4 |
| Lack of efficacy | 159 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Maintenance |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | No |
| Arm title | Arm A - Follow-up |

Arm description: -

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| | |
|------------------|---------------------------------|
| Arm title | Arm B1 - Maintenance Pemetrexed |
|------------------|---------------------------------|

Arm description:

Pemetrexed for patients with non-squamous cell carcinoma

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

Dosage and administration details:

Maintenance switch with pemetrexed IV 500 mg/m² every 3 weeks until progression or toxicity.

| | |
|------------------|----------------------------------|
| Arm title | ARM B2 - Maintenance Gemcitabine |
|------------------|----------------------------------|

Arm description:

Gemcitabine for patients with squamous cell carcinoma

| | |
|--|-----------------------|
| Arm type | Experimental |
| 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:

Maintenance switch with gemcitabine monotherapy IV (1150 mg/m² on Day 1, Day 8, cycles repeated every 21 days) until progression or unacceptable toxicity

| | |
|------------------|---------------------|
| Arm title | ARM B - Maintenance |
|------------------|---------------------|

Arm description:

Pemetrexed for patients with non-squamous cell carcinoma

Gemcitabine for patients with squamous cell carcinoma

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

Dosage and administration details:

Maintenance switch with pemetrexed IV 500 mg/m² every 3 weeks until progression or toxicity.

| | |
|--|-----------------------|
| 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:

Maintenance switch with gemcitabine monotherapy IV (1150 mg/m² on Day 1, Day 8, cycles repeated every 21 days) until progression or unacceptable toxicity

| Number of subjects in period 2 | Arm A - Follow-up | Arm B1 - Maintenance Pemetrexed | ARM B2 - Maintenance Gemcitabine |
|--------------------------------|-------------------|---------------------------------------|--|
| | | | |
| Started | 166 | 119 | 43 |
| Completed | 166 | 109 | 43 |
| Not completed | 0 | 10 | 0 |
| Not received treatment | - | - | - |
| Not received Pemetrexed | - | 10 | - |

| Number of subjects in period 2 | ARM B - Maintenance |
|--------------------------------|------------------------|
| Started | 162 |
| Completed | 152 |
| Not completed | 10 |
| Not received treatment | 10 |
| Not received Pemetrexed | - |

Period 3

| | |
|------------------------------|-----------------------|
| Period 3 title | Second line Erlotinib |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|---|----------------------------------|
| Arm title | Erlotinib |
| Arm description: | |
| Second line fixed with erlotinib in case of disease progression (RECIST 1.1). | |
| Arm type | Second line fixed with erlotinib |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Erlotinib 150 mg/day | |

| | |
|---------------------------------------|-----------|
| Number of subjects in period 3 | Erlotinib |
| Started | 173 |
| Completed | 173 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Induction |
|-----------------------|-----------|

Reporting group description: -

| Reporting group values | Induction | Total | |
|-------------------------|--------------|-------|--|
| Number of subjects | 627 | 627 | |
| Age categorical | | | |
| Units: Subjects | | | |
| From 70 to 79 | 486 | 486 | |
| From 80 to 89 | 141 | 141 | |
| Age continuous | | | |
| Units: years | | | |
| median | 76.4 | | |
| full range (min-max) | 70.0 to 89.4 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 152 | 152 | |
| Male | 475 | 475 | |
| Performans status (PS) | | | |
| Units: Subjects | | | |
| PS 0-1 | 535 | 535 | |
| PS 2 | 86 | 86 | |
| Not evaluated | 6 | 6 | |
| Stage | | | |
| Units: Subjects | | | |
| Stage III | 62 | 62 | |
| Stage IV | 565 | 565 | |
| Smocking status | | | |
| Units: Subjects | | | |
| Smoker | 535 | 535 | |
| Never Smocker | 92 | 92 | |
| Histology subtype | | | |
| Units: Subjects | | | |
| Adenocarcinoma | 401 | 401 | |
| Squamous cell | 178 | 178 | |
| Large Cell | 13 | 13 | |
| NOS | 26 | 26 | |
| Other | 9 | 9 | |
| Mini Mental Score (MMS) | | | |
| Units: MMS score | | | |
| median | 28.0 | | |
| full range (min-max) | 19.0 to 30.0 | - | |

End points

End points reporting groups

| | |
|------------------------------|---|
| Reporting group title | Paclitaxel - Carboplatin |
| Reporting group description: | - |
| Reporting group title | Arm A - Follow-up |
| Reporting group description: | - |
| Reporting group title | Arm B1 - Maintenance Pemetrexed |
| Reporting group description: | Pemetrexed for patients with non-squamous cell carcinoma |
| Reporting group title | ARM B2 - Maintenance Gemcitabine |
| Reporting group description: | Gemcitabine for patients with squamous cell carcinoma |
| Reporting group title | ARM B - Maintenance |
| Reporting group description: | Pemetrexed for patients with non-squamous cell carcinoma Gemcitabine for patients with squamous cell carcinoma |
| Reporting group title | Erlotinib |
| Reporting group description: | Second line fixed with erlotinib in case of disease progression (RECIST 1.1). |

Primary: Overall survival

| | |
|------------------------|--|
| End point title | Overall survival |
| End point description: | Time from randomisation to death from any cause. |
| End point type | Primary |
| End point timeframe: | 39.7 months (median follow-up) |

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 162 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 14.1 (12.0 to 17.0) | 14.0 (10.9 to 16.9) | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Overall survival |
| Statistical analysis description: | Time from randomisation to death from any cause. |
| Comparison groups | Arm A - Follow-up v ARM B - Maintenance |

| | |
|---|-------------------|
| Number of subjects included in analysis | 328 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.2 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Secondary: Number of maintenance cycles received

| | |
|--------------------------------|---------------------------------------|
| End point title | Number of maintenance cycles received |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 39.7 months (median follow-up) | |

| End point values | Arm B1 - Maintenance Pemetrexed | ARM B2 - Maintenance Gemcitabine | | |
|-------------------------------|---------------------------------------|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 109 | 43 | | |
| Units: number of cycles | | | | |
| median (full range (min-max)) | 4 (1 to 38) | 4 (1 to 31) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free survival

| | |
|--------------------------------|---------------------------|
| End point title | Progression Free survival |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| 39.7 months (median follow-up) | |

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|-------------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 162 | | |
| Units: months | | | | |
| median (full range (min-max)) | 2.7 (2.6 to 3.1) | 5.7 (4.8 to 7.1) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response from randomization

| | |
|--|---|
| End point title | Duration of response from randomization |
| End point description: Duration of the response or stabilization obtained from the maintenance therapy. | |
| End point type | Secondary |
| End point timeframe: 39.7 months (median follow-up) | |

| End point values | Arm A - Follow-up | Arm B1 - Maintenance Pemetrexed | ARM B2 - Maintenance Gemcitabine | ARM B - Maintenance |
|-------------------------------|-------------------|---------------------------------|----------------------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 166 | 119 | 43 | 162 |
| Units: months | | | | |
| median (full range (min-max)) | 2.7 (0 to 41.8) | 5.6 (0 to 45.8) | 6.8 (0 to 36.9) | 5.7 (0 to 45.8) |

Statistical analyses

No statistical analyses for this end point

Secondary: Patients receiving second line erlotinib

| | |
|--|--|
| End point title | Patients receiving second line erlotinib |
| End point description: | |
| End point type | Secondary |
| End point timeframe: 39.7 months (median follow-up) | |

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|-----------------------------|-------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 166 | 162 | | |
| Units: Number of subjects | 109 | 68 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Evalutation of clinical prognostic survival factors

| | |
|---|--|
| End point title | Evaluation of clinical prognostic survival factors |
| End point description: | |
| Univariate analysis of all stratification criteria for randomization. | |
| 0 to 1 : in favor of maintenance arm | |
| 1 to 2 : in favor of follow-up arm | |
| End point type | Secondary |
| End point timeframe: | |
| 39.7 months (median follow-up) | |

| End point values | Paclitaxel - Carboplatin | | | |
|-----------------------------------|--------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 627 | | | |
| Units: Hazard Ratio | | | | |
| number (confidence interval 95%) | | | | |
| ALL | 0.91 (0.71 to 1.17) | | | |
| ECOG Performans Status 0-1 | 1.03 (0.78 to 1.36) | | | |
| ECOG Performans Status 2 | 0.70 (0.40 to 1.23) | | | |
| Non-squamous cell carcinoma | 0.82 (0.61 to 1.09) | | | |
| Squamous cell carcinoma | 1.26 (0.78 to 2.05) | | | |
| Stable response after 4 cycles | 0.94 (0.67 to 1.33) | | | |
| Objective response after 4 cycles | 0.97 (0.68 to 1.39) | | | |
| Age : 80 years old and over | 1.01 (0.58 to 1.74) | | | |
| Age : < 80 years old | 0.90 (0.68 to 1.18) | | | |

Statistical analyses

No statistical analyses for this end point

Post-hoc: Response rate according to RECIST 1.1 - Second line

End point title Response rate according to RECIST 1.1 - Second line

End point description:

End point type Post-hoc

End point timeframe:

39.7 months (median follow-up)

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|-----------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 ^[1] | 103 ^[2] | | |
| Units: Number of subjects | | | | |
| Complete response | 1 | 1 | | |
| Partial response | 8 | 7 | | |
| Stable | 40 | 30 | | |
| Progression | 61 | 42 | | |
| Not done/Not evaluable | 5 | 5 | | |
| Missing | 18 | 18 | | |

Notes:

[1] - Patients with second-line systemic post-treatment

[2] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival from second line

End point title Overall Survival from second line

End point description:

End point type Post-hoc

End point timeframe:

39.7 months (median follow-up)

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 ^[3] | 103 ^[4] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.7 (8.8 to 14.9) | 9.2 (5.9 to 13.2) | | |

Notes:

[3] - Patients with second-line systemic post-treatment

[4] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression Free survival from second line

| | |
|-----------------|--|
| End point title | Progression Free survival from second line |
|-----------------|--|

End point description:

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

39.7 months (median follow-up)

| End point values | Arm A - Follow-up | ARM B - Maintenance | | |
|----------------------------------|--------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 133 ^[5] | 103 ^[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.9 (2.1 to 4) | 3.2 (2.2 to 4.8) | | |

Notes:

[5] - Patients with second-line systemic post-treatment

[6] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events have to be reported from inclusion to 30 day following the end of administration of study treatments.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Induction |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|-------------------|
| Reporting group title | Arm A - Follow-up |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|---------------------------------|
| Reporting group title | Arm B1 - Maintenance Pemetrexed |
|-----------------------|---------------------------------|

Reporting group description:

The safety population - Arm B Pemetrexed will be defined as all patients who received at least one dose of pemetrexed.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Arm B2 - Maintenance Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

The safety population - Arm B Gemcitabine will be defined as all patients who received at least one dose of Gemcitabine.

| Serious adverse events | Induction | Arm A - Follow-up | Arm B1 - Maintenance Pemetrexed |
|---|--------------------|-------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 220 / 623 (35.31%) | 2 / 166 (1.20%) | 38 / 109 (34.86%) |
| number of deaths (all causes) | 53 | 134 | 93 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |

| | | | |
|--|------------------|-----------------|-----------------|
| Hypertension | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 11 / 623 (1.77%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Venous thrombosis | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 9 / 623 (1.44%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 5 / 9 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|-----------------|-----------------|
| Chest pain | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| General physical health deterioration | | | |
| subjects affected / exposed | 34 / 623 (5.46%) | 1 / 166 (0.60%) | 8 / 109 (7.34%) |
| occurrences causally related to treatment / all | 14 / 37 | 0 / 1 | 3 / 8 |
| deaths causally related to treatment / all | 0 / 15 | 0 / 0 | 0 / 2 |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Inflammation | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Influenza like illness | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Malaise | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Oedema | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sense of oppression | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |

| | | | |
|---|------------------|-----------------|-----------------|
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Acute respiratory failure | | | |
| subjects affected / exposed | 4 / 623 (0.64%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 623 (2.09%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Haemoptysis | | | |
| subjects affected / exposed | 4 / 623 (0.64%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Haemothorax | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Hypercapnia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Laryngeal dyspnoea | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Lung disorder | | | |
| subjects affected / exposed | 12 / 623 (1.93%) | 0 / 166 (0.00%) | 6 / 109 (5.50%) |
| occurrences causally related to treatment / all | 5 / 12 | 0 / 0 | 1 / 6 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 2 |
| Pleural effusion | | | |
| subjects affected / exposed | 9 / 623 (1.44%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 12 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 oedema | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 distress | | | |
| subjects affected / exposed | 7 / 623 (1.12%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Mania | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 623 (1.12%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Fall | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Fracture | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 chemical | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Radius fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Skull fracture | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 | 7 / 623 (1.12%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 1 / 8 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Cardiomyopathy | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Tachycardia | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Cerebrovascular accident | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Coma | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Facial nerve disorder | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Motor dysfunction | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| 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 disorder | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Paralysis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| 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 | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 13 / 623 (2.09%) | 0 / 166 (0.00%) | 6 / 109 (5.50%) |
| occurrences causally related to treatment / all | 11 / 13 | 0 / 0 | 6 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone marrow failure | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (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 bone marrow aplasia | | | |
| subjects affected / exposed | 6 / 623 (0.96%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 12 / 623 (1.93%) | 0 / 166 (0.00%) | 3 / 109 (2.75%) |
| occurrences causally related to treatment / all | 13 / 13 | 0 / 0 | 3 / 3 |
| deaths causally related to treatment / all | 3 / 3 | 0 / 0 | 2 / 2 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Vertigo | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Colitis | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 623 (1.12%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 haemorrhage | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 1 |
| Inguinal hernia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hydrocholecystis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 6 / 623 (0.96%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Bone pain | | | |
| subjects affected / exposed | 4 / 623 (0.64%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 pain | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Infections and infestations | | | |
| Abscess | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 623 (0.64%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 colitis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes virus infection | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Herpes zoster | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Infection | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Lung infection | | | |
| subjects affected / exposed | 6 / 623 (0.96%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 5 / 7 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 | 4 / 623 (0.64%) | 0 / 166 (0.00%) | 2 / 109 (1.83%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate infection | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Pyelonephritis | | | |

| | | | |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 623 (0.32%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Sepsis | | | |
| subjects affected / exposed | 22 / 623 (3.53%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 14 / 22 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 5 / 11 | 0 / 0 | 1 / 1 |
| Septic shock | | | |
| subjects affected / exposed | 6 / 623 (0.96%) | 1 / 166 (0.60%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 6 / 6 | 0 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 1 | 1 / 1 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 623 (0.80%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 3 / 623 (0.48%) | 0 / 166 (0.00%) | 0 / 109 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 0 / 109 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 623 (0.00%) | 0 / 166 (0.00%) | 1 / 109 (0.92%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 0 / 109 (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 |

| | | | |
|---|--|--|--|
| Serious adverse events | Arm B2 - Maintenance Gemcitabine | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 24 / 43 (55.81%) | | |
| number of deaths (all causes) | 31 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Embolism | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous thrombosis | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sense of oppression | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Anaphylactic shock | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug hypersensitivity | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemothorax | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypercapnia | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngeal dyspnoea | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung disorder | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleural effusion | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumothorax | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory distress | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mania | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fall | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis chemical | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural complication | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac arrest | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiac failure | | | | |
| subjects affected / exposed | 4 / 43 (9.30%) | | | |
| occurrences causally related to treatment / all | 3 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cardiomyopathy | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Coronary artery disease | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myocardial infarction | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pericardial effusion | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Supraventricular tachycardia | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tachycardia | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coma | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial nerve disorder | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Facial paralysis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic stroke | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Loss of consciousness | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Motor dysfunction | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nervous system disorder | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paralysis | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral motor neuropathy | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral sensory neuropathy | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Presyncope | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 43 (4.65%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancytopenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric ulcer | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorder | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal ischaemia | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Melaena | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Oesophagitis | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stomatitis | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Umbilical hernia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hydrocholecystis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin toxicity | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Urinary retention | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------------------------|--|--|
| Infections and infestations Abscess subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 43 (0.00%) 0 / 0 0 / 0 | | |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 43 (2.33%) 1 / 1 0 / 0 | | |
| Catheter site infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 43 (2.33%) 1 / 1 0 / 0 | | |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 43 (2.33%) 0 / 1 0 / 0 | | |
| Clostridium colitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 43 (0.00%) 0 / 0 0 / 0 | | |
| Cystitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 43 (0.00%) 0 / 0 0 / 0 | | |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 43 (0.00%) 0 / 0 0 / 0 | | |
| Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 43 (2.33%) 1 / 1 0 / 0 | | |
| Herpes virus infection | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes zoster | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung infection | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peritonitis | | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumocystis jirovecii pneumonia | | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 3 / 43 (6.98%) | | | |
| occurrences causally related to treatment / all | 1 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prostate infection | | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Acidosis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 43 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 43 (2.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Induction | Arm A - Follow-up | Arm B1 - Maintenance Pemetrexed |
|---|--------------------|--------------------|------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 602 / 623 (96.63%) | 135 / 166 (81.33%) | 106 / 109 (97.25%) |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 318 / 623 (51.04%) | 42 / 166 (25.30%) | 57 / 109 (52.29%) |
| occurrences (all) | 320 | 58 | 118 |
| Chest pain | | | |
| subjects affected / exposed | 36 / 623 (5.78%) | 12 / 166 (7.23%) | 7 / 109 (6.42%) |
| occurrences (all) | 38 | 12 | 8 |
| Fatigue | | | |
| subjects affected / exposed | 34 / 623 (5.46%) | 4 / 166 (2.41%) | 8 / 109 (7.34%) |
| occurrences (all) | 34 | 5 | 12 |
| General physical health deterioration | | | |
| subjects affected / exposed | 37 / 623 (5.94%) | 2 / 166 (1.20%) | 16 / 109 (14.68%) |
| occurrences (all) | 39 | 2 | 17 |
| Oedema peripheral | | | |
| subjects affected / exposed | 51 / 623 (8.19%) | 5 / 166 (3.01%) | 30 / 109 (27.52%) |
| occurrences (all) | 52 | 8 | 65 |
| Pyrexia | | | |
| subjects affected / exposed | 30 / 623 (4.82%) | 3 / 166 (1.81%) | 15 / 109 (13.76%) |
| occurrences (all) | 30 | 5 | 23 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 106 / 623 (17.01%) | 33 / 166 (19.88%) | 16 / 109 (14.68%) |
| occurrences (all) | 106 | 43 | 23 |
| Dyspnoea | | | |
| subjects affected / exposed | 159 / 623 (25.52%) | 40 / 166 (24.10%) | 30 / 109 (27.52%) |
| occurrences (all) | 159 | 52 | 52 |
| Lung disorder | | | |
| subjects affected / exposed | 12 / 623 (1.93%) | 0 / 166 (0.00%) | 6 / 109 (5.50%) |
| occurrences (all) | 12 | 0 | 6 |
| Productive cough | | | |
| subjects affected / exposed | 24 / 623 (3.85%) | 3 / 166 (1.81%) | 8 / 109 (7.34%) |
| occurrences (all) | 24 | 3 | 8 |

| | | | |
|--|---------------------------|-------------------------|--------------------------|
| Chest pain subjects affected / exposed occurrences (all) | 5 / 623 (0.80%) 5 | 4 / 166 (2.41%) 4 | 1 / 109 (0.92%) 1 |
| Investigations | | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 15 / 623 (2.41%) 15 | 0 / 166 (0.00%) 0 | 13 / 109 (11.93%) 21 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 22 / 623 (3.53%) 22 | 0 / 166 (0.00%) 0 | 19 / 109 (17.43%) 27 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 21 / 623 (3.37%) 21 | 0 / 166 (0.00%) 0 | 8 / 109 (7.34%) 11 |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 32 / 623 (5.14%) 33 | 3 / 166 (1.81%) 5 | 11 / 109 (10.09%) 12 |
| Weight decreased subjects affected / exposed occurrences (all) | 78 / 623 (12.52%) 78 | 6 / 166 (3.61%) 6 | 11 / 109 (10.09%) 16 |
| Cardiac disorders | | | |
| Cardiac failure subjects affected / exposed occurrences (all) | 8 / 623 (1.28%) 8 | 0 / 166 (0.00%) 0 | 2 / 109 (1.83%) 2 |
| Nervous system disorders | | | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 60 / 623 (9.63%) 60 | 18 / 166 (10.84%) 29 | 9 / 109 (8.26%) 18 |
| Paraesthesia subjects affected / exposed occurrences (all) | 97 / 623 (15.57%) 103 | 14 / 166 (8.43%) 23 | 17 / 109 (15.60%) 23 |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 449 / 623 (72.07%) 450 | 62 / 166 (37.35%) 79 | 81 / 109 (74.31%) 186 |
| Febrile neutropenia | | | |

| | | | |
|--|--------------------|-----------------|-------------------|
| subjects affected / exposed | 17 / 623 (2.73%) | 0 / 166 (0.00%) | 8 / 109 (7.34%) |
| occurrences (all) | 17 | 0 | 8 |
| Leukopenia | | | |
| subjects affected / exposed | 79 / 623 (12.68%) | 0 / 166 (0.00%) | 11 / 109 (10.09%) |
| occurrences (all) | 79 | 0 | 16 |
| Lymphopenia | | | |
| subjects affected / exposed | 68 / 623 (10.91%) | 5 / 166 (3.01%) | 11 / 109 (10.09%) |
| occurrences (all) | 68 | 8 | 16 |
| Neutropenia | | | |
| subjects affected / exposed | 363 / 623 (58.27%) | 6 / 166 (3.61%) | 50 / 109 (45.87%) |
| occurrences (all) | 370 | 6 | 88 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 277 / 623 (44.46%) | 6 / 166 (3.61%) | 41 / 109 (37.61%) |
| occurrences (all) | 279 | 7 | 65 |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 623 (0.16%) | 0 / 166 (0.00%) | 13 / 109 (11.93%) |
| occurrences (all) | 1 | 0 | 21 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 100 / 623 (16.05%) | 4 / 166 (2.41%) | 16 / 109 (14.68%) |
| occurrences (all) | 100 | 6 | 24 |
| Diarrhoea | | | |
| subjects affected / exposed | 117 / 623 (18.78%) | 3 / 166 (1.81%) | 15 / 109 (13.76%) |
| occurrences (all) | 118 | 3 | 21 |
| Nausea | | | |
| subjects affected / exposed | 172 / 623 (27.61%) | 2 / 166 (1.20%) | 28 / 109 (25.69%) |
| occurrences (all) | 175 | 2 | 42 |
| Vomiting | | | |
| subjects affected / exposed | 76 / 623 (12.20%) | 1 / 166 (0.60%) | 11 / 109 (10.09%) |
| occurrences (all) | 60 | 1 | 15 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 90 / 623 (14.45%) | 6 / 166 (3.61%) | 3 / 109 (2.75%) |
| occurrences (all) | 90 | 9 | 7 |
| Pruritus | | | |

| | | | |
|---|-------------------------|------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 11 / 623 (1.77%) 11 | 2 / 166 (1.20%) 3 | 7 / 109 (6.42%) 8 |
| Rash subjects affected / exposed occurrences (all) | 9 / 623 (1.44%) 9 | 3 / 166 (1.81%) 3 | 9 / 109 (8.26%) 12 |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 66 / 623 (10.59%) 66 | 15 / 166 (9.04%) 22 | 25 / 109 (22.94%) 56 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 36 / 623 (5.78%) 41 | 10 / 166 (6.02%) 11 | 5 / 109 (4.59%) 7 |
| Back pain subjects affected / exposed occurrences (all) | 33 / 623 (5.30%) 33 | 12 / 166 (7.23%) 17 | 14 / 109 (12.84%) 17 |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 10 / 623 (1.61%) 10 | 0 / 166 (0.00%) 0 | 4 / 109 (3.67%) 6 |
| Pain in extremity subjects affected / exposed occurrences (all) | 21 / 623 (3.37%) 21 | 7 / 166 (4.22%) 7 | 5 / 109 (4.59%) 6 |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 20 / 623 (3.21%) 21 | 7 / 166 (4.22%) 7 | 11 / 109 (10.09%) 14 |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 623 (0.48%) 3 | 1 / 166 (0.60%) 1 | 9 / 109 (8.26%) 15 |
| Erysipelas subjects affected / exposed occurrences (all) | 1 / 623 (0.16%) 1 | 0 / 166 (0.00%) 0 | 10 / 109 (9.17%) 17 |
| Lung infection subjects affected / exposed occurrences (all) | 9 / 623 (1.44%) 9 | 5 / 166 (3.01%) 7 | 7 / 109 (6.42%) 7 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------------|-----------------------|-------------------------|
| Decreased appetite subjects affected / exposed occurrences (all) | 133 / 623 (21.35%) 135 | 8 / 166 (4.82%) 10 | 26 / 109 (23.85%) 41 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 41 / 623 (6.58%) 41 | 6 / 166 (3.61%) 6 | 10 / 109 (9.17%) 16 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 42 / 623 (6.74%) 42 | 3 / 166 (1.81%) 4 | 7 / 109 (6.42%) 9 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 16 / 623 (2.57%) 16 | 2 / 166 (1.20%) 2 | 6 / 109 (5.50%) 7 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 35 / 623 (5.62%) 35 | 1 / 166 (0.60%) 1 | 4 / 109 (3.67%) 9 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 31 / 623 (4.98%) 31 | 4 / 166 (2.41%) 5 | 3 / 109 (2.75%) 3 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | Arm B2 - Maintenance Gemcitabine | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 42 / 43 (97.67%) | | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 16 / 43 (37.21%) 25 | | |
| Chest pain subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Fatigue subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 12 | | |
| General physical health deterioration subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Oedema peripheral | | | |

| | | | |
|--|--|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 43 (18.60%)</p> <p>11</p> <p>9 / 43 (20.93%)</p> <p>10</p> | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dyspnoea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Lung disorder</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Productive cough</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>11 / 43 (25.58%)</p> <p>18</p> <p>14 / 43 (32.56%)</p> <p>20</p> <p>3 / 43 (6.98%)</p> <p>3</p> <p>2 / 43 (4.65%)</p> <p>2</p> <p>0 / 43 (0.00%)</p> <p>0</p> | | |
| <p>Investigations</p> <p>Alanine aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Aspartate aminotransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Blood alkaline phosphatase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Gamma-glutamyltransferase increased</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Weight decreased</p> | <p>4 / 43 (9.30%)</p> <p>9</p> <p>4 / 43 (9.30%)</p> <p>6</p> <p>1 / 43 (2.33%)</p> <p>3</p> <p>1 / 43 (2.33%)</p> <p>3</p> | | |

| | | | |
|--|--|--|--|
| subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 4 | | |
| Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 4 | | |
| Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 15 6 / 43 (13.95%) 20 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 34 / 43 (79.07%) 77 2 / 43 (4.65%) 2 6 / 43 (13.95%) 7 8 / 43 (18.60%) 12 19 / 43 (44.19%) 25 23 / 43 (53.49%) 38 | | |
| Eye disorders Lacrimation increased subjects affected / exposed occurrences (all) | 0 / 43 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|--|-----------------------|--|--|
| Constipation subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 3 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 2 | | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 3 | | |
| Renal and urinary disorders | | | |
| Renal failure subjects affected / exposed occurrences (all) | 5 / 43 (11.63%) 11 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 43 (4.65%) 5 | | |
| Back pain subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 3 / 43 (6.98%) 3 | | |

| | | | |
|--|--|--|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 5 | | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Erysipelas subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all) | 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 2 / 43 (4.65%) 2 3 / 43 (6.98%) 3 | | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) | 4 / 43 (9.30%) 8 3 / 43 (6.98%) 5 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 0 / 43 (0.00%) 0 3 / 43 (6.98%) 5 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 12 August 2013 | <ul style="list-style-type: none">- Clarification of inclusion/exclusion criteria<ul style="list-style-type: none">* Patients with active or symptomatic central nervous system metastases are ineligible. Patients with a history of symptomatic central nervous system metastases or spinal cord compression may be included if they have been treated (surgery or radiotherapy) and have become asymptomatic. Oral corticosteroids are allowed provided that the dose has been stable for at least 4 weeks prior to the start of treatment.* The criterion for radiation therapy is moved to maintenance eligibility criteria and updated for: "No concurrent radiation therapy, except for palliative localized non-spinal bone radiation therapy, with a 2 week delay between the administration of gemcitabine and the start of radiation therapy or the end of radiation therapy before the start of treatment, which may be shortened to 8 days if required by the patient's clinical condition. In the case of spinal irradiation, irradiation should be avoided as much as possible within 4 weeks after the administration of gemcitabine."- Clarification of the time frame to start treatment: the maximum time between inclusion and the start of induction treatment is 2 weeks. The maximum time between Day 1 of the 4th cycle of induction therapy and Day 1 of maintenance is 42 days. The second line should start no later than 3 weeks after the assessment showing progression.- Correction of the summary table of examinations:<ul style="list-style-type: none">* Deletion of the geriatric depression scale at each evaluation (to be done only at inclusion and after 4 cycles of induction).* Biology at Day 8 and Day 15 are only to be done for patients receiving chemotherapy.- Chemotherapy doses will be capped at 400 mg/m² for carboplatin and at 2m² of body surface area in general.- Calvert's formula will be used for calculation of carboplatin dose. |
| 18 August 2014 | <ul style="list-style-type: none">- Correction of the criterion on peripheral neuropathy (possible inclusion of patients with grade 1 neuropathy).- Patients with a history of prostate cancer less than 5 years old may be included under certain conditions.- Clarification of the tumor assessment at randomization: thoracic CT with adrenal sections, abdominal ultrasound and/or abdominal CT and brain CT or MRI are to be performed at randomization (those exams will be the reference for assessment during maintenance and observation). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Choice of the geriatric indexes was somewhat arbitrary ; Relatively high number of missing values pertaining to the geriatric indexes at the time of randomisation ; Erlotinib is no longer recommended as salvage therapy in pts without EGFR mutations

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/32898792>