



Clinical trial results:

Phase III international, randomized study of Trabectedin plus Pegylated Liposomal Doxorubicin (PLD) versus Carboplatin plus PLD in patients with ovarian cancer progressing within 6-12 months of last platinum

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2010-022949-17 |
| Trial protocol | IT GB FI BE NL DK DE ES AT NO |
| Global end of trial date | 09 April 2021 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 15 September 2022 |
| First version publication date | 15 September 2022 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | ET-D-009-10 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Istituto di Ricerche Farmacologiche Mario Negri IRCCS |
| Sponsor organisation address | Via Mario Negri 2, Milan, Italy, 20156 |
| Public contact | Eliaana Rulli, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 0039 0239014645, eliana.rulli@marionegri.it |
| Scientific contact | Eliaana Rulli, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, 0039 0239014645, eliana.rulli@marionegri.it |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 April 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 April 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 April 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the combination of trabectedin (Yondelis®) and pegylated liposomal doxorubicin (PLD) prolongs overall survival (OS) over carboplatin and PLD in patients with relapsed ovarian cancer progressing within 6-12 months after end of last platinum.

Protection of trial subjects:

NA

Background therapy:

In both arms PLD was administered as background therapy

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 08 January 2014 |
| 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 | Netherlands: 24 |
| Country: Number of subjects enrolled | Norway: 5 |
| Country: Number of subjects enrolled | Spain: 108 |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | Austria: 22 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Denmark: 15 |
| Country: Number of subjects enrolled | Finland: 25 |
| Country: Number of subjects enrolled | Germany: 58 |
| Country: Number of subjects enrolled | Italy: 283 |
| Country: Number of subjects enrolled | Switzerland: 42 |
| Worldwide total number of subjects | 617 |
| EEA total number of subjects | 550 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|-----|
| wk | |
| 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) | 330 |
| From 65 to 84 years | 285 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

The randomization started in Dec2011 but had to be put onto temporary hold just a month later (with one patient randomized) due to the worldwide shortage of PLD. AIFA approved the study restart on Aug 2013 whereas the Central EC approved the study restart on Sept 2013. Patients' accrual recommenced on Jan 8th 2014 and ended on Sept18th 2017.

Pre-assignment

Screening details:

NA

Period 1

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

Arms

| | |
|--|------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ARM A: Carboplatin+PLD |
| Arm description: - | |
| Arm type | Active comparator |
| Investigational medicinal product name | carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

PLD 30 mg/m² i.v. as a 1-hour infusion followed by carboplatin AUC 5 i.v. as a 30 min infusion on Day 1 every 4 weeks. A 4-week schedule defines a cycle of treatment

| | |
|--|--|
| Arm title | ARM B: Trabectedin+PLD |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | trabectedin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

PLD 30 mg/m² i.v. infusion immediately followed by trabectedin 1.1 mg/m² 3-hour i.v. infusion on Day 1 every 3 weeks. A 3-week schedule defines a cycle of treatment.

| Number of subjects in period 1 | ARM A: Carboplatin+PLD | ARM B: Trabectedin+PLD |
|---------------------------------------|---------------------------|---------------------------|
| Started | 306 | 311 |
| Completed | 306 | 311 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | overall trial |
| Reporting group description: - | |

| Reporting group values | overall trial | Total | |
|--|---------------|-------|--|
| Number of subjects | 617 | 617 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 330 | 330 | |
| From 65-84 years | 285 | 285 | |
| 85 years and over | 2 | 2 | |
| Age continuous | | | |
| Units: years | | | |
| median | 64 | | |
| inter-quartile range (Q1-Q3) | 55 to 70 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 617 | 617 | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Intention to treat |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

the ITT analysis set included all subjects who provided informed consent and were randomized to either carboplatin+PLD arm or trabectedin+PLD arm, without major deviations of the eligibility criteria. Subjects were considered in the randomization arm regardless of the treatment they received.

| | |
|----------------------------|---------------------|
| Subject analysis set title | safety analysis set |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

the Safety Analysis Set included all subjects of ITT analysis set who received at least one dose of treatment. Subjects were considered in the arm of the treatment they actually received.

| Reporting group values | Intention to treat | safety analysis set | |
|--|--------------------|---------------------|--|
| Number of subjects | 611 | 598 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |

| | | | |
|--|----------|----------|--|
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 327 | 317 | |
| From 65-84 years | 282 | 279 | |
| 85 years and over | 2 | 2 | |
| Age continuous | | | |
| Units: years | | | |
| median | 64 | 64 | |
| inter-quartile range (Q1-Q3) | 55 to 71 | 55 to 71 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | | |

End points

End points reporting groups

| | |
|---|------------------------|
| Reporting group title | ARM A: Carboplatin+PLD |
| Reporting group description: - | |
| Reporting group title | ARM B: Trabectedin+PLD |
| Reporting group description: - | |
| Subject analysis set title | Intention to treat |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| the ITT analysis set included all subjects who provided informed consent and were randomized to either carboplatin+PLD arm or trabectedin+PLD arm, without major deviations of the eligibility criteria. Subjects were considered in the randomization arm regardless of the treatment they received. | |
| Subject analysis set title | safety analysis set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| the Safety Analysis Set included all subjects of ITT analysis set who received at least one dose of treatment. Subjects were considered in the arm of the treatment they actually received. | |

Primary: overall survival

| | |
|---|------------------|
| End point title | overall survival |
| End point description: | |
| End point type | Primary |
| End point timeframe: | |
| from randomization to death or end of trial | |

| End point values | ARM A: Carboplatin+PLD | ARM B: Trabectedin+PLD | Intention to treat | |
|-----------------------------|---------------------------|---------------------------|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 304 | 307 | 611 | |
| Units: patients | 231 | 240 | 471 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | overall survival |
| Comparison groups | ARM A: Carboplatin+PLD v ARM B: Trabectedin+PLD |
| Number of subjects included in analysis | 611 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.13 |

| Confidence interval | |
|---------------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.94 |
| upper limit | 1.35 |

Notes:

[1] - For the primary analysis, OS between treatment arms will be compared by the log-rank test. Cox regression will be used to calculate the risk reduction and to evaluate the influence of the randomization variables and other potential prognostic factors on the time to event endpoint.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from informed consent signature until 30 days after the last administration of study treatments

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 22 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------|
| Reporting group title | Arm A |
|-----------------------|-------|

Reporting group description:

Carboplatin + PLD

| | |
|-----------------------|-------|
| Reporting group title | Arm B |
|-----------------------|-------|

Reporting group description:

Trabectedin + PLD

| Serious adverse events | Arm A | Arm B | |
|---|-------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 66 / 294 (22.45%) | 130 / 304 (42.76%) | |
| number of deaths (all causes) | 228 | 238 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Colon cancer | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant bowel obstruction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Ascites | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites, pyrexia, pancytopenia, deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Metastasis to lung, pharyngitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myelodysplastic syndrome | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 3 / 304 (0.99%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock haemorrhagic | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Portacath insertion | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stent placement | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Obstruction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia, vomiting | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease Progression | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Extravasation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue, cachexia, hepatic enzyme increased | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 3 / 294 (1.02%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 8 / 304 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Reproductive system and breast disorders | | | |
| Metrorrhagia, asthenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 5 / 304 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion, pulmonary embolism | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 6 / 304 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Electrocardiogram ST segment elevation | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip Fracture | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting, phlebitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular systolic dysfunction | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain chest | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 12 / 304 (3.95%) | |
| occurrences causally related to treatment / all | 1 / 1 | 11 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis, pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia, stomatitis, platelet count decreased | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia, anaemia, otitis media | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 6 / 304 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia, anaemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia, thrombocytopenia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 294 (0.68%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia, pyrexia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsisClostridium difficile infection Pancytopenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 294 (1.36%) | 3 / 304 (0.99%) | |
| occurrences causally related to treatment / all | 7 / 7 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased, febrile neutropenia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain, decreased appetite | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | | | |
| subjects affected / exposed | 6 / 294 (2.04%) | 8 / 304 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain, ileal obstruction, | | | |

| | | | |
|---|-----------------|-----------------|--|
| constipation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute Pancreatitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowel obstruction | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowel occlusion | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhea | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorder | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 4 / 294 (1.36%) | 4 / 304 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 8 / 294 (2.72%) | 5 / 304 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal occlusion | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 4 / 304 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 6 / 304 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, asthenia, decreased appetite | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, vomiting | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 5 / 304 (1.64%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, vomiting, constipation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, vomiting, constipation, abdominal pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, vomiting, hyponatraemia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Occlusion | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis, nausea, vomiting | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal perforation | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Subileus | | | |
| subjects affected / exposed | 2 / 294 (0.68%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|--|-----------------|------------------|--|
| subjects affected / exposed | 1 / 294 (0.34%) | 10 / 304 (3.29%) | |
| occurrences causally related to treatment / all | 1 / 1 | 10 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting, fatigue | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatobiliary disorders, vomiting, pyrexia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis acute | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis acute | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Increased Bilirubin, neutropenia, thrombocytopenia, anemia | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea, hypertransaminasaemia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Palmar-plantar erythrodysaesthesia syndrome | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia, back pain | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc compression | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 5 / 304 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 2 / 304 (0.66%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 6 / 304 (1.97%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyoderma | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 0 / 304 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 294 (0.34%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Shock septic | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metabolism and nutrition disorders | | | |
| Hyponatremia | | | |
| subjects affected / exposed | 0 / 294 (0.00%) | 1 / 304 (0.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A | Arm B | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 251 / 294 (85.37%) | 262 / 304 (86.18%) | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 10 / 294 (3.40%) | 16 / 304 (5.26%) | |
| occurrences (all) | 16 | 22 | |
| Neuropathy | | | |
| subjects affected / exposed | 41 / 294 (13.95%) | 39 / 304 (12.83%) | |
| occurrences (all) | 44 | 45 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 84 / 294 (28.57%) | 72 / 304 (23.68%) | |
| occurrences (all) | 136 | 123 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 72 / 294 (24.49%) | 41 / 304 (13.49%) | |
| occurrences (all) | 152 | 71 | |
| Leukopenia | | | |
| subjects affected / exposed | 40 / 294 (13.61%) | 44 / 304 (14.47%) | |
| occurrences (all) | 86 | 102 | |
| Neutropenia | | | |
| subjects affected / exposed | 112 / 294 (38.10%) | 156 / 304 (51.32%) | |
| occurrences (all) | 307 | 373 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 61 / 294 (20.75%) | 74 / 304 (24.34%) | |
| occurrences (all) | 115 | 136 | |
| Fatigue | | | |
| subjects affected / exposed | 77 / 294 (26.19%) | 74 / 304 (24.34%) | |
| occurrences (all) | 102 | 124 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 25 / 294 (8.50%) | 31 / 304 (10.20%) | |
| occurrences (all) | 38 | 54 | |
| Oedema | | | |

| | | | |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 9 / 294 (3.06%) 11 | 16 / 304 (5.26%) 21 | |
| Pain subjects affected / exposed occurrences (all) | 17 / 294 (5.78%) 22 | 33 / 304 (10.86%) 43 | |
| Pyrexia subjects affected / exposed occurrences (all) | 13 / 294 (4.42%) 19 | 34 / 304 (11.18%) 42 | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 15 / 294 (5.10%) 17 | 8 / 304 (2.63%) 8 | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 111 / 294 (37.76%) 196 | 144 / 304 (47.37%) 281 | |
| Stomatitis subjects affected / exposed occurrences (all) | 32 / 294 (10.88%) 42 | 41 / 304 (13.49%) 66 | |
| Vomiting subjects affected / exposed occurrences (all) | 60 / 294 (20.41%) 100 | 94 / 304 (30.92%) 162 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 31 / 294 (10.54%) 36 | 36 / 304 (11.84%) 52 | |
| Constipation subjects affected / exposed occurrences (all) | 62 / 294 (21.09%) 98 | 93 / 304 (30.59%) 127 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 50 / 294 (17.01%) 71 | 53 / 304 (17.43%) 65 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 9 / 294 (3.06%) 11 | 18 / 304 (5.92%) 27 | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|-------------------------|--------------------------|--|
| Cough subjects affected / exposed occurrences (all) | 15 / 294 (5.10%) 16 | 17 / 304 (5.59%) 23 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 18 / 294 (6.12%) 20 | 33 / 304 (10.86%) 40 | |
| Hepatobiliary disorders Cholestasis subjects affected / exposed occurrences (all) | 10 / 294 (3.40%) 22 | 17 / 304 (5.59%) 26 | |
| Hepatotoxicity subjects affected / exposed occurrences (all) | 16 / 294 (5.44%) 31 | 85 / 304 (27.96%) 213 | |
| Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 24 / 294 (8.16%) 26 | 36 / 304 (11.84%) 45 | |
| Dry skin subjects affected / exposed occurrences (all) | 15 / 294 (5.10%) 15 | 10 / 304 (3.29%) 10 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 24 / 294 (8.16%) 39 | 29 / 304 (9.54%) 41 | |
| Metabolism and nutrition disorders Appetite disorder subjects affected / exposed occurrences (all) | 34 / 294 (11.56%) 46 | 40 / 304 (13.16%) 53 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|-----------------|---|-------------------|
| 01 January 2012 | worldwide shortage of Pegylated Liposomal Doxorubicin (PLD - Caelyx®) | 17 September 2013 |

Notes:

Limitations and caveats

None reported