



Clinical trial results:

A Randomized, Open-label, Multicenter, Phase 3 Study to Compare the Efficacy and Safety of Eribulin with Dacarbazine in Subjects with Soft Tissue Sarcoma

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-024483-17 |
| Trial protocol | BE DE CZ GB AT DK ES IT |
| Global end of trial date | 10 August 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 27 February 2020 |
| First version publication date | 27 February 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | E7389-G000-309 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01327885 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Eisai Medical Research Inc. |
| Sponsor organisation address | 155 Tice Boulevard, Woodcliff Lake, United States, 07677 |
| Public contact | Eisai Medical Information, Eisai Inc., +1 1-888-274-2378, esi_oncmedinfo@eisai.com |
| Scientific contact | Eisai Medical Information, Eisai Inc., +1 1-888-274-2378, esi_oncmedinfo@eisai.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 August 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 10 August 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival (OS) in subjects with advanced soft tissue sarcoma (STS) (one of two subtypes: adipocytic sarcoma [ADI] or leiomyosarcoma [LMS]) when treated with eribulin (Arm A) or dacarbazine (Arm B).

Protection of trial subjects:

This study was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (World Medical Association, 2008)
- International Council on Harmonisation (ICH) E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions were reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP Subject Information and Informed Consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 10 March 2011 |
| 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: 11 |
| Country: Number of subjects enrolled | Poland: 1 |
| Country: Number of subjects enrolled | Romania: 7 |
| Country: Number of subjects enrolled | Spain: 23 |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | Austria: 7 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | Czech Republic: 10 |
| Country: Number of subjects enrolled | Denmark: 7 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | France: 65 |
| Country: Number of subjects enrolled | Germany: 16 |
| Country: Number of subjects enrolled | Italy: 38 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | United States: 157 |
| Country: Number of subjects enrolled | Brazil: 20 |
| Country: Number of subjects enrolled | Korea, Republic of: 17 |
| Country: Number of subjects enrolled | Israel: 14 |
| Country: Number of subjects enrolled | Thailand: 5 |
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Singapore: 4 |
| Country: Number of subjects enrolled | Argentina: 3 |
| Country: Number of subjects enrolled | Russian Federation: 1 |
| Worldwide total number of subjects | 452 |
| EEA total number of subjects | 211 |

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) | 356 |
| From 65 to 84 years | 96 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

There were 594 subjects screened for entry into the study. Of these subjects, 452 were randomized into the study and 142 were identified as screen failures.

Period 1

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

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A: Eribulin mesylate |

Arm description:

Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m^2) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Eribulin mesylate |
| Investigational medicinal product code | E7389 |
| Other name | Halaven |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

Eribulin mesylate at a dose of $1.4 \text{ mg}/\text{m}^2$ was administered IV as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

| | |
|------------------|--------------------|
| Arm title | Arm B: Dacarbazine |
|------------------|--------------------|

Arm description:

Dacarbazine at a dose of $850 \text{ mg}/\text{m}^2$, $1000 \text{ mg}/\text{m}^2$, or $1200 \text{ mg}/\text{m}^2$ (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Dacarbazine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dacarbazine at a dose of $850 \text{ mg}/\text{m}^2$, $1000 \text{ mg}/\text{m}^2$, or $1200 \text{ mg}/\text{m}^2$ (as selected by the PI or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

| Number of subjects in period 1 | Arm A: Eribulin mesylate | Arm B: Dacarbazine |
|---|--------------------------|--------------------|
| Started | 228 | 224 |
| Completed | 0 | 0 |
| Not completed | 228 | 224 |
| Clinical progression | 24 | 27 |
| Participant choice | 5 | 10 |
| Disease progression-according to RECIST | 173 | 165 |
| Adverse event, non-fatal | 14 | 10 |
| Not specified | 8 | 6 |
| Study terminated by sponsor | - | 1 |
| Withdrawal of consent from study | 3 | 4 |
| Not treated | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Arm A: Eribulin mesylate |
|-----------------------|--------------------------|

Reporting group description:

Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m²) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

| | |
|-----------------------|--------------------|
| Reporting group title | Arm B: Dacarbazine |
|-----------------------|--------------------|

Reporting group description:

Dacarbazine at a dose of 850 mg/m², 1000 mg/m², or 1200 mg/m² (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

| Reporting group values | Arm A: Eribulin mesylate | Arm B: Dacarbazine | Total |
|--|--------------------------|--------------------|-------|
| Number of subjects | 228 | 224 | 452 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 55.6 | 55.7 | |
| standard deviation | ± 11.01 | ± 10.35 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 161 | 142 | 303 |
| Male | 67 | 82 | 149 |

End points

End points reporting groups

| | |
|--|--------------------------|
| Reporting group title | Arm A: Eribulin mesylate |
| Reporting group description: Eribulin mesylate at a dose of 1.4 milligram per square meter (mg/m ²) was administered intravenously (IV) as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle. | |
| Reporting group title | Arm B: Dacarbazine |
| Reporting group description: Dacarbazine at a dose of 850 mg/m ² , 1000 mg/m ² , or 1200 mg/m ² (as selected by the principal investigator [PI] or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle. | |

Primary: Overall Survival (OS)

| | |
|--|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: OS was defined as the time in months from the date of treatment start until death, regardless of cause. In the absence of confirmation of death, subjects were censored either at the date that subject was last known to be alive or the date of study cut-off, whichever was earlier. Subjects who died on the date of randomization had a survival time of 0.5 day. Allocation of randomization numbers were performed based upon the following stratification factors: (a) Histology (ADI or LMS), (b) Region (Region 1: United States of America and Canada; or Region 2: Western Europe, Australia, Israel; or Region 3: Eastern Europe, Latin America, and Asia), and (c) Number of prior regimens for advanced STS (2 or >2 prior regimens). Full analysis set (FAS) (Intent-to-Treat [ITT] analysis set) included all subjects who were randomized. | |
| End point type | Primary |
| End point timeframe: From date of randomization until date of death from any cause, up to approximately 5 years 5 months. | |

| End point values | Arm A: Eribulin mesylate | Arm B: Dacarbazine | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 224 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 13.5 (10.9 to 15.6) | 11.5 (9.6 to 13.0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | OS |
| Statistical analysis description: Statistical analysis was designed to detect superiority of Arm A (eribulin) over Arm B (dacarbazine). OS was compared between the two treatment arms using a two-sided stratified log-rank test at a nominal significance level of 0.0455 (adjusted for the interim analysis). This was the primary analysis that was performed when the target number of events (~353 deaths) was observed. | |
| Comparison groups | Arm B: Dacarbazine v Arm A: Eribulin mesylate |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 452 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0169 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.768 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.618 |
| upper limit | 0.954 |

Notes:

[1] - The P-value was calculated by 2-sided log-rank test as stratified by histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Progression-free Survival (PFS)

| | |
|-----------------|---------------------------------|
| End point title | Progression-free Survival (PFS) |
|-----------------|---------------------------------|

End point description:

PFS was defined as the time from the date of randomization to the date of first documentation of disease progression, or date of death (whichever occurred first). The date of disease progression was defined as the date of radiologic disease progression as assessed by the investigator or designee based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Subjects who did not have an event (that is subjects who were lost to follow-up or who did not progress or die at the date of data cut-off), were censored. Subjects who discontinued study treatment without disease progression were censored on the date of their last radiological assessment (scan date). FAS (ITT analysis set) included all subjects who were randomized.

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

End point timeframe:

Randomization (day 1) to the date of first documentation of disease progression, or date of death (whichever occurred first), approximately up to 5 years 5 months.

| End point values | Arm A: Eribulin mesylate | Arm B: Dacarbazine | | |
|----------------------------------|--------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 224 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.6 (1.9 to 2.8) | 2.6 (1.8 to 2.7) | | |

Statistical analyses

| | |
|----------------------------|---------------------------------|
| Statistical analysis title | Progression-free Survival (PFS) |
|----------------------------|---------------------------------|

Statistical analysis description:

The PFS and PFS rate at 3, 6, and 12 months (95% confidence interval[CI]) was calculated using Kaplan-Meier (K-M) product-limit method and Greenwood Formula. PFS was compared between the treatment arms using two-sided stratified log-rank test, stratified by histology, geographic region, and number of prior regimens for advanced STS.

| | |
|-------------------|---|
| Comparison groups | Arm B: Dacarbazine v Arm A: Eribulin mesylate |
|-------------------|---|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 452 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2287 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.877 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.085 |

Notes:

[2] - P-value was calculated by 2-sided log-rank test, as stratified by histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Progression-free Rate at 12 Weeks (PFR12wks)

| | |
|---|--|
| End point title | Progression-free Rate at 12 Weeks (PFR12wks) |
| End point description: | |
| The PFR12wks was defined as the percentage of subjects who were still alive without disease progression at 12 weeks from the date of randomization. Tumor assessment by the investigator or designee was based on RECIST 1.1. FAS (ITT analysis set) included all subjects who were randomized. | |
| End point type | Secondary |
| End point timeframe: | |
| From date of randomization start until Week 12 | |

| End point values | Arm A: Eribulin mesylate | Arm B: Dacarbazine | | |
|-----------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 224 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 33.3 (27.2 to 39.9) | 28.6 (22.8 to 35.0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Progression-Free Rate at 12 Weeks (PFR12wks) |
| Statistical analysis description: | |
| The PFR12wks was compared between the treatment arms using stratified Cochran-Mantel-Haenszel (CMH) chi-square test stratified by histology, geographic region, and number of prior regimens for advanced STS. The odds ratio between eribulin and dacarbazine was calculated by stratified CMH method. The stratified factors were as described above. The 2-sided 95% CI of the odds ratio is based on asymptotic normal approximation. | |
| Comparison groups | Arm A: Eribulin mesylate v Arm B: Dacarbazine |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 452 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.253 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.9 |

Notes:

[3] - The P-value was calculated using the stratified CMH method, the stratified factors included histology, geographic region, and number of prior regimens for advanced STS.

Secondary: Clinical Benefit Rate (CBR)

| | |
|-----------------|-----------------------------|
| End point title | Clinical Benefit Rate (CBR) |
|-----------------|-----------------------------|

End point description:

CBR was defined as the percentage of subjects who have best overall response (BOR) of CR, or PR, or duration of stable disease (dSD) greater than or equal to 11 weeks, between Arm A and Arm B. CBR was estimated by treatment arm based on the tumor response evaluation performed by the PI or designee according to RECIST 1.1. CR was defined as disappearance of all target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of the longest diameter. FAS (ITT analysis set) included all subjects who were randomized.

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

End point timeframe:

From date of treatment start (Day 1) until disease progression, development of unacceptable toxicity, withdrawal of consent, subject's choice to stop study treatment, up to approximately 5 years 5 months

| End point values | Arm A: Eribulin mesylate | Arm B: Dacarbazine | | |
|-----------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 228 | 224 | | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 46.1 (39.5 to 52.8) | 47.8 (41.1 to 54.5) | | |

Statistical analyses

| | |
|----------------------------|-----------------------------|
| Statistical analysis title | Clinical Benefit Rate (CBR) |
|----------------------------|-----------------------------|

Statistical analysis description:

The CBR was compared between the treatment arms using stratified CMH chi-square test stratified by histology, geographic region, and number of prior regimens for advanced STS. The odds ratio between eribulin and dacarbazine was calculated by stratified CMH method. The stratified factors were as described above. The 2-sided 95% CI of odds ratio is based on asymptotic normal approximation.

| | |
|-------------------|---|
| Comparison groups | Arm A: Eribulin mesylate v Arm B: Dacarbazine |
|-------------------|---|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 452 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.741 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.7 |
| upper limit | 1.4 |

Notes:

[4] - The P-value was calculated using the CMH method. The stratified factors were histology, geographic region, and number of prior regimens for advanced STS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of first dose up to 30 days after the last dose of study treatment, up to approximately 5 years 5 months

Adverse event reporting additional description:

Treatment-emergent AEs were reported. Safety analysis set included all subjects who were randomized, received at least one dose of study treatment, and had at least one post-baseline safety evaluation. All treated subjects were included in the safety analysis set and analyzed in the treatment arm for the study drug they actually received.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.1 |

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Arm A: Eribulin mesylate |
|-----------------------|--------------------------|

Reporting group description:

Eribulin mesylate at a dose of 1.4 mg/m² was administered IV as a bolus infusion over 2-5 minutes on Days 1 and 8 of every 21-day treatment cycle.

| | |
|-----------------------|--------------------|
| Reporting group title | Arm B: Dacarbazine |
|-----------------------|--------------------|

Reporting group description:

Dacarbazine at a dose of 850 mg/m², 1000 mg/m², or 1200 mg/m² (as selected by the PI or designee prior to randomization according to the subject's clinical status) was administered as an IV infusion over 15-30 minutes (or up to 60 minutes as per institutional guidelines) on Day 1 of every 21-day treatment cycle.

| Serious adverse events | Arm A: Eribulin mesylate | Arm B: Dacarbazine | |
|---|--------------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 76 / 226 (33.63%) | 71 / 224 (31.70%) | |
| number of deaths (all causes) | 13 | 8 | |
| number of deaths resulting from adverse events | 10 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to lung | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metastases to neck | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastatic pain | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myxoid liposarcoma | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leiomyosarcoma | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant ascites | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 3 / 224 (1.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 10 / 226 (4.42%) | 4 / 224 (1.79%) | |
| occurrences causally related to treatment / all | 4 / 13 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | | |
|---|---|-----------------|-----------------|--|
| Asthenia | subjects affected / exposed | 3 / 226 (1.33%) | 1 / 224 (0.45%) | |
| | occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | subjects affected / exposed | 2 / 226 (0.88%) | 1 / 224 (0.45%) | |
| | occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| | deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Fatigue | subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| | occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | | |
| | Hypersensitivity | | | |
| | subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug hypersensitivity | | | | |
| | subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| | occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| | Pulmonary embolism | | | |
| | subjects affected / exposed | 4 / 226 (1.77%) | 1 / 224 (0.45%) | |
| | occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | | |
| | subjects affected / exposed | 4 / 226 (1.77%) | 2 / 224 (0.89%) | |
| | occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| | deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 4 / 224 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 226 (0.00%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 7 / 7 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| 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 | | | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nervous system disorders | | | |
| Convulsion | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Monoplegia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 11 / 226 (4.87%) | 10 / 224 (4.46%) | |
| occurrences causally related to treatment / all | 18 / 18 | 12 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 226 (2.21%) | 9 / 224 (4.02%) | |
| occurrences causally related to treatment / all | 4 / 5 | 9 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Leukopenia | | | |
| subjects affected / exposed | 3 / 226 (1.33%) | 3 / 224 (1.34%) | |
| occurrences causally related to treatment / all | 4 / 4 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 2 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 3 / 224 (1.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 13 / 224 (5.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 19 / 19 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 226 (1.77%) | 4 / 224 (1.79%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 4 / 226 (1.77%) | 5 / 224 (2.23%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 226 (0.88%) | 3 / 224 (1.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestine perforation | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal distension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal fistula | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| 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 | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 226 (0.88%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Biliary dilatation | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 226 (1.77%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 226 (1.33%) | 2 / 224 (0.89%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis bacterial | | | |
| subjects affected / exposed | 2 / 226 (0.88%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis bacterial | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection fungal | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Serratia bacteraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vestibular neuronitis | | | |
| subjects affected / exposed | 0 / 226 (0.00%) | 1 / 224 (0.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 226 (0.44%) | 0 / 224 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A: Eribulin mesylate | Arm B: Dacarbazine | |
|---|--------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 223 / 226 (98.67%) | 218 / 224 (97.32%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 13 / 226 (5.75%) | 4 / 224 (1.79%) | |
| occurrences (all) | 13 | 4 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 98 / 226 (43.36%) | 86 / 224 (38.39%) | |
| occurrences (all) | 191 | 127 | |
| Pyrexia | | | |
| subjects affected / exposed | 58 / 226 (25.66%) | 28 / 224 (12.50%) | |
| occurrences (all) | 85 | 35 | |
| Asthenia | | | |
| subjects affected / exposed | 46 / 226 (20.35%) | 51 / 224 (22.77%) | |
| occurrences (all) | 82 | 80 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 27 / 226 (11.95%) | 17 / 224 (7.59%) | |
| occurrences (all) | 30 | 21 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 39 / 226 (17.26%) | 28 / 224 (12.50%) | |
| occurrences (all) | 50 | 33 | |
| Dyspnoea | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 34 / 226 (15.04%) 40 | 33 / 224 (14.73%) 37 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 12 / 226 (5.31%) 15 | 5 / 224 (2.23%) 5 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 22 / 226 (9.73%) 24 | 10 / 224 (4.46%) 10 | |
| Anxiety subjects affected / exposed occurrences (all) | 12 / 226 (5.31%) 13 | 14 / 224 (6.25%) 16 | |
| Investigations | | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 21 / 226 (9.29%) 53 | 5 / 224 (2.23%) 6 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 19 / 226 (8.41%) 90 | 12 / 224 (5.36%) 34 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 18 / 226 (7.96%) 57 | 8 / 224 (3.57%) 10 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 16 / 226 (7.08%) 71 | 15 / 224 (6.70%) 56 | |
| Electrocardiogram QT prolonged subjects affected / exposed occurrences (all) | 14 / 226 (6.19%) 23 | 11 / 224 (4.91%) 13 | |
| Blood lactate dehydrogenase increased subjects affected / exposed occurrences (all) | 12 / 226 (5.31%) 20 | 7 / 224 (3.13%) 8 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 2 / 226 (0.88%) 8 | 17 / 224 (7.59%) 45 | |
| Nervous system disorders | | | |

| | | | |
|---|--------------------------|---------------------------|--|
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 46 / 226 (20.35%) 81 | 8 / 224 (3.57%) 8 | |
| Headache subjects affected / exposed occurrences (all) | 41 / 226 (18.14%) 55 | 21 / 224 (9.38%) 25 | |
| Dizziness subjects affected / exposed occurrences (all) | 21 / 226 (9.29%) 21 | 16 / 224 (7.14%) 16 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 20 / 226 (8.85%) 28 | 7 / 224 (3.13%) 11 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 18 / 226 (7.96%) 34 | 5 / 224 (2.23%) 6 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia subjects affected / exposed occurrences (all) | 95 / 226 (42.04%) 234 | 51 / 224 (22.77%) 139 | |
| Anaemia subjects affected / exposed occurrences (all) | 66 / 226 (29.20%) 151 | 68 / 224 (30.36%) 149 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 13 / 226 (5.75%) 27 | 60 / 224 (26.79%) 191 | |
| Leukopenia subjects affected / exposed occurrences (all) | 36 / 226 (15.93%) 109 | 22 / 224 (9.82%) 65 | |
| Eye disorders | | | |
| Lacrimation increased subjects affected / exposed occurrences (all) | 18 / 226 (7.96%) 29 | 1 / 224 (0.45%) 1 | |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 91 / 226 (40.27%) 138 | 106 / 224 (47.32%) 153 | |
| Constipation | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 70 / 226 (30.97%) | 58 / 224 (25.89%) | |
| occurrences (all) | 102 | 69 | |
| Abdominal pain | | | |
| subjects affected / exposed | 42 / 226 (18.58%) | 32 / 224 (14.29%) | |
| occurrences (all) | 50 | 44 | |
| Vomiting | | | |
| subjects affected / exposed | 43 / 226 (19.03%) | 50 / 224 (22.32%) | |
| occurrences (all) | 52 | 60 | |
| Diarrhoea | | | |
| subjects affected / exposed | 38 / 226 (16.81%) | 35 / 224 (15.63%) | |
| occurrences (all) | 46 | 42 | |
| Stomatitis | | | |
| subjects affected / exposed | 31 / 226 (13.72%) | 11 / 224 (4.91%) | |
| occurrences (all) | 51 | 12 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 19 / 226 (8.41%) | 13 / 224 (5.80%) | |
| occurrences (all) | 22 | 15 | |
| Dyspepsia | | | |
| subjects affected / exposed | 18 / 226 (7.96%) | 7 / 224 (3.13%) | |
| occurrences (all) | 21 | 8 | |
| Abdominal distension | | | |
| subjects affected / exposed | 16 / 226 (7.08%) | 12 / 224 (5.36%) | |
| occurrences (all) | 19 | 16 | |
| Dry mouth | | | |
| subjects affected / exposed | 12 / 226 (5.31%) | 4 / 224 (1.79%) | |
| occurrences (all) | 12 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 79 / 226 (34.96%) | 6 / 224 (2.68%) | |
| occurrences (all) | 106 | 6 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 33 / 226 (14.60%) | 31 / 224 (13.84%) | |
| occurrences (all) | 37 | 37 | |
| Myalgia | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 23 / 226 (10.18%) | 17 / 224 (7.59%) | |
| occurrences (all) | 29 | 19 | |
| Pain in extremity | | | |
| subjects affected / exposed | 20 / 226 (8.85%) | 18 / 224 (8.04%) | |
| occurrences (all) | 27 | 24 | |
| Arthralgia | | | |
| subjects affected / exposed | 19 / 226 (8.41%) | 13 / 224 (5.80%) | |
| occurrences (all) | 23 | 14 | |
| Muscle spasms | | | |
| subjects affected / exposed | 13 / 226 (5.75%) | 7 / 224 (3.13%) | |
| occurrences (all) | 19 | 8 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 12 / 226 (5.31%) | 11 / 224 (4.91%) | |
| occurrences (all) | 13 | 11 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 23 / 226 (10.18%) | 11 / 224 (4.91%) | |
| occurrences (all) | 28 | 14 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 20 / 226 (8.85%) | 9 / 224 (4.02%) | |
| occurrences (all) | 25 | 12 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 43 / 226 (19.03%) | 43 / 224 (19.20%) | |
| occurrences (all) | 56 | 52 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 23 / 226 (10.18%) | 9 / 224 (4.02%) | |
| occurrences (all) | 35 | 11 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 17 / 226 (7.52%) | 6 / 224 (2.68%) | |
| occurrences (all) | 38 | 8 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 25 May 2012 | Amendment 01: The protocol was amended to update that 1. Subjects should have received at least two standard systemic regimens for advanced STS one of which must have included an anthracycline (unless contraindicated) in inclusion criterion #3. 2. Addition of exclusion of temozolomide from prior therapy in exclusion criterion #3. 3. Removal of exclusion criterion #4, 4. Clarified that only serious and potentially life-threatening cardiac arrhythmia would require exclusion from the protocol in exclusion criterion #6. 5. Excluding subjects with a high probability for Long QT Syndrome (LQTS) added in exclusion criterion #7. 6. Exclude serious concomitant illness or infectious disease requiring treatment to exclude infectious disease not requiring treatment but with significant risks for myelosuppressive complications associated with chemotherapy added in exclusion criterion #9. 7. Histologically confirmed complete excision of carcinoma in situ exempted from exclusion criterion #10. 8. Study treatment administration on Day 1 of Cycle 1 and each cycle thereafter. 9. Allowed for dacarbazine dilution up to 500 milliliter (mL) and infusion rate up to 60 minutes. 10. Included instructions for temporary discontinuation of treatment, dose reduction, or resumption of treatment in tabulated form. 11. Permanent discontinuation of study treatment required if unable to administer a scheduled dose of study treatment for more than 21 days due to treatment-related toxicity. 12. Criteria for both arms added for eribulin mesilate and dacarbazine and amendment of serious adverse event (SAE) reporting timeframe to require SAEs to be reported to the Sponsor within 24 hours (and not within 1 business day). |
| 08 August 2012 | Amendment 02 Subjects in Arm A (eribulin) who had a Grade 3 or Grade 4 QTc interval prolongation were to have study drug permanently discontinued. |
| 01 December 2015 | Amendment 03: The protocol was amended to update in the Extension Phase of the study, following the database lock for the primary analysis, ongoing subjects on study treatment in the dacarbazine arm are allowed to cross over to the eribulin arm at the discretion of the investigator decision, frequency of tumor assessments will be permitted to change from every 9 weeks to a frequency at the investigator's discretion. For subjects who have discontinued study treatment without disease progression, tumor assessments will no longer be required, Sponsor may decide to terminate survival follow-up of all subjects during the Extension Phase after the completion of the primary analysis and when the sponsor considers the data from the primary analysis to be sufficiently mature to no longer require further collection of survival data. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported