



Clinical trial results:

A Multicenter Phase II Clinical Trial of Lurbinectedin (PM01183) in Selected Advanced Solid Tumors.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-003773-42 |
| Trial protocol | ES BE SE GB DE |
| Global end of trial date | 18 September 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 03 October 2021 |
| First version publication date | 03 October 2021 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | PM1183-B-005-14 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02454972 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pharma Mar, S.A. |
| Sponsor organisation address | Avenida de los Reyes, 1 Polígono Industrial "La Mina", Colmenar Viejo, Madrid, Spain, 28770 |
| Public contact | Clinical Development, Department of PharmaMar's Oncology, Business Unit., Pharmamar, S.A., 0034 91846 60 00, clinicaltrials@pharmamar.com |
| Scientific contact | Clinical Development, Department of PharmaMar's Oncology, Business Unit., Pharmamar, S.A., 0034 91846 60 00, clinicaltrials@pharmamar.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 | 16 November 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 September 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 September 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of lurbinectedin (PM01183) in terms of overall response rate (ORR), according to RECIST v 1.1 in the following advanced solid tumors: small cell lung cancer (SCLC), head and neck carcinoma (H&N), neuroendocrine tumors (NETs), biliary tract carcinoma, endometrial carcinoma, BRCA 1/2-associated metastatic breast carcinoma, carcinoma of unknown primary site, germ cell tumors (GCTs) and Ewing's family of tumors (EFTs).

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

All patients received standard antiemetic prophylaxis before each treatment infusion. The i.v. formulations of these agents were used in this setting:

- Corticosteroids (dexamethasone 8 mg or equivalent).
- Serotonin (5-HT₃) antagonists (ondansetron 8 mg or equivalent).
- Extended treatment with oral 5-HT₃ antagonists and oral dexamethasone for two consecutive days.
- If necessary, and in addition to the above, administration of 10 mg of oral or i.v. metoclopramide (or equivalent) every eight hours.

Aprepitant and equivalent agents (e.g., fosaprepitant) were forbidden in patients treated with lurbinectedin.

For the purpose of safety evaluations, an optimal prophylaxis was defined as all the aforementioned allowed medications at their respectively maximum dose.

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 25 August 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 77 |
| Country: Number of subjects enrolled | Switzerland: 11 |
| Country: Number of subjects enrolled | Spain: 154 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | Belgium: 14 |
| Country: Number of subjects enrolled | France: 64 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Italy: 8 |

| | |
|------------------------------------|-----|
| Worldwide total number of subjects | 345 |
| EEA total number of subjects | 244 |

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) | 226 |
| From 65 to 84 years | 119 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The first patient registration was on 25 August 2015 and the first study treatment administration was on 25 August 2015. The last patient registration was on 30 November 2018 and the last study treatment administration was on 29 November 2019. The date of last follow-up (cutoff-date) was 18 September 2020.

Pre-assignment

Screening details:

Age ≥ 18 years; signed informed consent; Pathologically proven diagnosis; Patients had to have received no more than two prior chemotherapy-containing lines; ECOG PS ≤ 2 ; Adequate major organ function; Washout periods prior to Day 1 of Cycle 1.

Period 1

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

Arms

| | |
|------------------------------|--------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Biliary tract carcinoma cohort |

Arm description:

Patients with Pathologically proven diagnosis of biliary tract carcinoma

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|------------------|--|
| Arm title | Carcinoma of unknown primary site cohort |
|------------------|--|

Arm description:

Patients with pathologically proven diagnosis of carcinoma of unknown primary site

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks

= one treatment cycle).

| | |
|--|--|
| Arm title | Endometrial carcinoma cohort |
| Arm description: Patients with pathologically proven diagnosis of endometrial carcinoma | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|---|--|
| Arm title | Ewing's Family of Tumors cohort |
| Arm description: Patients with pathologically proven diagnosis of Ewing's Family of Tumors | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|--|--|
| Arm title | Germ Cell Tumors cohort |
| Arm description: Patients with pathologically proven diagnosis of Germ Cell Tumors, excluding immature teratoma, or teratoma with malignant transformation. | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|---|--|
| Arm title | Head and Neck Carcinoma cohort |
| Arm description: Patients with Pathologically proven diagnosis of Head and Neck Carcinoma. Salivary glands tumors were excluded. | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|---|---|
| Arm title | BRCA1/2-associated metastatic breast carcinoma cohort |
| Arm description: Patients with pathologically proven diagnosis of BRCA1/2-associated metastatic breast carcinoma | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|--|--|
| Arm title | Neuroendocrine Tumors cohort |
| Arm description: Patients with Pathologically proven diagnosis of Neuroendocrine Tumors, grade 2 and 3 according to World Health Organization (WHO) classification. | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not

exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| | |
|---|--|
| Arm title | Small Cell Lung Cancer cohort |
| Arm description: | |
| Patients with pathologically proven diagnosis of small cell lung cancer | |
| Arm type | Experimental |
| Investigational medicinal product name | Lurbinectedin |
| Investigational medicinal product code | PM1183 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Lurbinectedin was administered over a minimum total volume of 100 mL of solution for infusion (either on 5% glucose or 0.9% sodium chloride), through a central catheter, or over a minimum total volume of 250 mL if administered through a peripheral line, always over one hour at a fixed infusion rate. Starting dose was 3.2 mg/m². Dose was capped at body surface area (BSA) of 2.0 m² (i.e., dose did not exceed 6.4 mg).

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| Number of subjects in period 1 ^[1] | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort |
|---|--------------------------------|--|------------------------------|
| | | | |
| Started | 19 | 19 | 73 |
| Completed | 0 | 0 | 0 |
| Not completed | 19 | 19 | 73 |
| Physician decision | - | 1 | 2 |
| Consent withdrawn by subject | - | 1 | 5 |
| Non treatment-related adverse event | 2 | - | 1 |
| Death | - | - | 5 |
| Treatment-related adverse events | - | 1 | 1 |
| Patient moves to compassionate use | - | - | - |
| Progressive disease | 17 | 16 | 59 |
| Multiple delay/holds on treatment | - | - | - |

| Number of subjects in period 1 ^[1] | Ewing's Family of Tumors cohort | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort |
|---|---------------------------------|-------------------------|--------------------------------|
| | | | |
| Started | 28 | 23 | 15 |
| Completed | 0 | 0 | 0 |
| Not completed | 28 | 23 | 15 |
| Physician decision | 1 | 2 | - |
| Consent withdrawn by subject | 2 | 3 | 2 |
| Non treatment-related adverse event | - | - | 1 |

| | | | |
|------------------------------------|----|----|----|
| Death | 1 | - | - |
| Treatment-related adverse events | - | 2 | - |
| Patient moves to compassionate use | - | - | - |
| Progressive disease | 23 | 16 | 12 |
| Multiple delay/holds on treatment | 1 | - | - |

| Number of subjects in period 1 ^[1] | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort | Small Cell Lung Cancer cohort |
|---|---|------------------------------|-------------------------------|
| | | | |
| Started | 21 | 32 | 105 |
| Completed | 0 | 0 | 0 |
| Not completed | 21 | 32 | 105 |
| Physician decision | - | 1 | 4 |
| Consent withdrawn by subject | - | 1 | 2 |
| Non treatment-related adverse event | - | 1 | - |
| Death | - | - | 2 |
| Treatment-related adverse events | - | 2 | 2 |
| Patient moves to compassionate use | 2 | - | 11 |
| Progressive disease | 19 | 27 | 84 |
| Multiple delay/holds on treatment | - | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 10 patients have never been treated (3 endometrial carcinoma cohort, 1 Ewing's family of tumors cohort, 1 germ cell tumors cohort and 5 small cell lung cancer cohort)

Baseline characteristics

| Reporting groups | |
|--|---|
| Reporting group title | Biliary tract carcinoma cohort |
| Reporting group description: | |
| Patients with Pathologically proven diagnosis of biliary tract carcinoma | |
| Reporting group title | Carcinoma of unknown primary site cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of carcinoma of unknown primary site | |
| Reporting group title | Endometrial carcinoma cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of endometrial carcinoma | |
| Reporting group title | Ewing's Family of Tumors cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of Ewing's Family of Tumors | |
| Reporting group title | Germ Cell Tumors cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of Germ Cell Tumors, excluding immature teratoma, or teratoma with malignant transformation. | |
| Reporting group title | Head and Neck Carcinoma cohort |
| Reporting group description: | |
| Patients with Pathologically proven diagnosis of Head and Neck Carcinoma. Salivary glands tumors were excluded. | |
| Reporting group title | BRCA1/2-associated metastatic breast carcinoma cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of BRCA1/2-associated metastatic breast carcinoma | |
| Reporting group title | Neuroendocrine Tumors cohort |
| Reporting group description: | |
| Patients with Pathologically proven diagnosis of Neuroendocrine Tumors, grade 2 and 3 according to World Health Organization (WHO) classification. | |
| Reporting group title | Small Cell Lung Cancer cohort |
| Reporting group description: | |
| Patients with pathologically proven diagnosis of small cell lung cancer | |

| Reporting group values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort |
|------------------------|--------------------------------|--|------------------------------|
| Number of subjects | 19 | 19 | 73 |
| Age categorical | | | |
| Units: Subjects | | | |
| 18-40 years | 2 | 1 | 2 |
| 41-64 years | 11 | 9 | 35 |
| ≥65 years | 6 | 9 | 36 |
| Age continuous | | | |
| Units: years | | | |
| median | 61 | 61 | 64 |
| full range (min-max) | 34 to 74 | 27 to 78 | 32 to 80 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 11 | 73 |
| Male | 9 | 8 | 0 |

| | | | |
|--|----|----|----|
| Race | | | |
| Units: Subjects | | | |
| White | 13 | 15 | 45 |
| Not race available | 6 | 4 | 22 |
| Black of African American | 0 | 0 | 5 |
| Asian | 0 | 0 | 1 |
| American Indian or Alaska native | 0 | 0 | 0 |
| ECOG PS | | | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead | | | |
| Units: Subjects | | | |
| PS 0 | 5 | 8 | 32 |
| PS 1 | 14 | 10 | 35 |
| PS 2 | 0 | 1 | 6 |
| Albumin | | | |
| Units: Subjects | | | |
| <3.5 g/dL | 5 | 4 | 9 |
| ≥3.5 g/dL | 14 | 15 | 64 |
| Stage at diagnosis | | | |
| Units: Subjects | | | |
| Early | 0 | 0 | 23 |
| Locally advanced | 4 | 0 | 27 |
| Metastatic | 15 | 19 | 23 |
| Sites at baseline | | | |
| Units: Subjects | | | |
| <3 sites | 6 | 12 | 40 |
| ≥3 sites | 13 | 7 | 33 |
| Prior surgery | | | |
| Units: Subjects | | | |
| Yes | 2 | 2 | 62 |
| No | 17 | 17 | 11 |
| Prior radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 2 | 8 | 39 |
| No | 17 | 11 | 34 |
| Best response to last therapy | | | |
| According to the RECIST v.1.1, Complete Response: Disappearance of all target lesions; Partial Response: ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline; Progressive disease: ≥20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD | | | |
| Units: Subjects | | | |
| Complete response | 0 | 3 | 7 |
| Partial reponse | 4 | 4 | 20 |
| Stable disease | 7 | 5 | 13 |
| Progression disease | 8 | 4 | 15 |
| Unknown | 0 | 3 | 18 |

| | | | |
|---|---------------|---------------|---------------|
| Systemic lines Units: Subjects | | | |
| 1 line | 13 | 12 | 54 |
| 2 lines | 6 | 7 | 15 |
| 3 lines | 0 | 0 | 3 |
| 4 or more lines | 0 | 0 | 1 |
| Advanced chemotherapy lines | | | |
| 999, not applicable | | | |
| Units: Subjects | | | |
| 0 lines | 19 | 0 | 15 |
| 1 line | 0 | 12 | 47 |
| 2 lines | 0 | 7 | 8 |
| 3 lines | 0 | 0 | 2 |
| 4 or more lines | 0 | 0 | 1 |
| Weight Units: Kg | | | |
| median | 72.2 | 65.0 | 70.0 |
| full range (min-max) | 45.0 to 115.0 | 50.1 to 108.2 | 42.5 to 140.8 |
| Height Units: cm | | | |
| median | 168 | 164.5 | 161 |
| full range (min-max) | 148 to 187 | 141 to 187 | 143 to 180 |
| Body surface area Units: m ² | | | |
| median | 1.9 | 1.8 | 1.8 |
| full range (min-max) | 1.4 to 2.4 | 1.5 to 2.4 | 1.3 to 2.6 |
| Albumin Units: g/dL | | | |
| median | 3.7 | 3.7 | 4.1 |
| full range (min-max) | 2.9 to 4.7 | 3.2 to 4.4 | 2.7 to 4.7 |
| Number of sites at baseline Units: Number of sites | | | |
| median | 3 | 2 | 2 |
| full range (min-max) | 2 to 6 | 1 to 4 | 1 to 7 |
| Time from diagnosis to registration Units: months | | | |
| median | 8.4 | 10.8 | 18.4 |
| full range (min-max) | 3.8 to 23.0 | 4.6 to 62.9 | 4.3 to 190.9 |
| Time from advanced disease to registration Units: month | | | |
| median | 10.6 | 999 | 17.5 |
| full range (min-max) | 6.3 to 23.0 | 999 to 999 | 0.9 to 97.0 |
| Time to progression to last prior therapy Units: months | | | |
| median | 5.2 | 3.9 | 8.0 |
| full range (min-max) | 1.0 to 14.0 | 0.9 to 22.9 | 1.4 to 23.5 |
| Time from last progression disease before study entry Units: weeks | | | |
| median | 3.0 | 2.6 | 2.9 |
| full range (min-max) | 0.3 to 6.7 | 0.1 to 33.7 | 0.0 to 24.6 |

| Reporting group values | Ewing's Family of Tumors cohort | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort |
|--|--|--------------------------------|---------------------------------------|
| Number of subjects | 28 | 23 | 15 |
| Age categorical Units: Subjects | | | |
| 18-40 years | 19 | 12 | 1 |
| 41-64 years | 8 | 8 | 8 |
| ≥65 years | 1 | 3 | 6 |
| Age continuous Units: years | | | |
| median | 33 | 36 | 62 |
| full range (min-max) | 18 to 74 | 21 to 73 | 39 to 81 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 7 | 1 |
| Male | 16 | 16 | 14 |
| Race Units: Subjects | | | |
| White | 21 | 15 | 12 |
| Not race available | 4 | 7 | 2 |
| Black of African American | 1 | 0 | 0 |
| Asian | 2 | 1 | 1 |
| American Indian or Alaska native | 0 | 0 | 0 |
| ECOG PS | | | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead | | | |
| Units: Subjects | | | |
| PS 0 | 11 | 2 | 5 |
| PS 1 | 16 | 19 | 10 |
| PS 2 | 1 | 2 | 0 |
| Albumin Units: Subjects | | | |
| <3.5 g/dL | 2 | 4 | 3 |
| ≥3.5 g/dL | 26 | 19 | 12 |
| Stage at diagnosis Units: Subjects | | | |
| Early | 14 | 8 | 4 |
| Locally advanced | 5 | 1 | 7 |
| Metastatic | 9 | 14 | 4 |
| Sites at baseline Units: Subjects | | | |
| <3 sites | 18 | 7 | 10 |
| ≥3 sites | 10 | 16 | 5 |
| Prior surgery Units: Subjects | | | |
| Yes | 20 | 21 | 9 |

| | | | |
|---|---------------|---------------|---------------|
| No | 8 | 2 | 6 |
| Prior radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 20 | 7 | 11 |
| No | 8 | 16 | 4 |
| Best response to last therapy | | | |
| According to the RECIST v.1.1, Complete Response: Disappearance of all target lesions; Partial Response: $\geq 30\%$ decrease in the sum of the longest diameters of target lesions compared with baseline; Progressive disease: $\geq 20\%$ increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD | | | |
| Units: Subjects | | | |
| Complete response | 0 | 0 | 0 |
| Partial reponse | 0 | 2 | 5 |
| Stable disease | 0 | 5 | 2 |
| Progression disease | 0 | 15 | 7 |
| Unknown | 28 | 1 | 1 |
| Systemic lines | | | |
| Units: Subjects | | | |
| 1 line | 5 | 0 | 5 |
| 2 lines | 15 | 4 | 8 |
| 3 lines | 5 | 8 | 2 |
| 4 or more lines | 3 | 11 | 0 |
| Advanced chemotherapy lines | | | |
| 999, not applicable | | | |
| Units: Subjects | | | |
| 0 lines | 5 | 0 | 0 |
| 1 line | 7 | 1 | 5 |
| 2 lines | 13 | 4 | 9 |
| 3 lines | 3 | 8 | 1 |
| 4 or more lines | 0 | 10 | 0 |
| Weight | | | |
| Units: Kg | | | |
| median | 77.0 | 78.5 | 73.0 |
| full range (min-max) | 51.0 to 127.7 | 59.0 to 116.3 | 49.0 to 107.0 |
| Height | | | |
| Units: cm | | | |
| median | 173 | 177 | 170 |
| full range (min-max) | 155 to 193 | 157 to 190 | 155 to 186 |
| Body surface area | | | |
| Units: m ² | | | |
| median | 1.9 | 2.0 | 1.8 |
| full range (min-max) | 1.6 to 2.4 | 1.7 to 2.4 | 1.5 to 2.2 |
| Albumin | | | |
| Units: g/dL | | | |
| median | 4.2 | 4.1 | 3.8 |
| full range (min-max) | 3.3 to 4.9 | 3.2 to 4.8 | 3.0 to 4.4 |
| Number of sites at baseline | | | |
| Units: Number of sites | | | |
| median | 2 | 3 | 2 |
| full range (min-max) | 1 to 6 | 1 to 4 | 1 to 6 |
| Time from diagnosis to registration | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| Units: months median full range (min-max) | 28.6 6.9 to 140.5 | 48.2 7.3 to 308.8 | 19.5 2.9 to 426.1 |
| Time from advanced disease to registration Units: month median full range (min-max) | 20.4 0.4 to 54.2 | 999 999 to 999 | 18.4 9.7 to 72.7 |
| Time to progression to last prior therapy Units: months median full range (min-max) | 8.7 0.4 to 25.8 | 2.7 0.8 to 29.6 | 4.6 1.4 to 26.1 |
| Time from last progression disease before study entry Units: weeks median full range (min-max) | 2.1 0.0 to 7.1 | 1.4 0.3 to 6.4 | 2.4 0.0 to 24.7 |

| Reporting group values | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort | Small Cell Lung Cancer cohort |
|--|---|------------------------------|-------------------------------|
| Number of subjects | 21 | 32 | 105 |
| Age categorical Units: Subjects | | | |
| 18-40 years | 5 | 5 | 2 |
| 41-64 years | 14 | 14 | 66 |
| ≥65 years | 2 | 13 | 37 |
| Age continuous Units: years median full range (min-max) | 45 29 to 73 | 63 23 to 77 | 60 40 to 83 |
| Gender categorical Units: Subjects | | | |
| Female | 21 | 12 | 42 |
| Male | 0 | 20 | 63 |
| Race Units: Subjects | | | |
| White | 18 | 24 | 79 |
| Not race available | 3 | 7 | 24 |
| Black of African American | 0 | 0 | 1 |
| Asian | 0 | 0 | 1 |
| American Indian or Alaska native | 0 | 1 | 0 |
| ECOG PS | | | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead | | | |
| Units: Subjects | | | |
| PS 0 | 18 | 8 | 38 |
| PS 1 | 2 | 23 | 59 |

| | | | |
|---|---------------|---------------|---------------|
| PS 2 | 1 | 1 | 8 |
| Albumin | | | |
| Units: Subjects | | | |
| <3.5 g/dL | 1 | 9 | 13 |
| ≥3.5 g/dL | 20 | 23 | 92 |
| Stage at diagnosis | | | |
| Units: Subjects | | | |
| Early | 10 | 5 | 3 |
| Locally advanced | 6 | 8 | 29 |
| Metastatic | 5 | 19 | 73 |
| Sites at baseline | | | |
| Units: Subjects | | | |
| <3 sites | 12 | 13 | 26 |
| ≥3 sites | 9 | 19 | 79 |
| Prior surgery | | | |
| Units: Subjects | | | |
| Yes | 19 | 11 | 2 |
| No | 2 | 21 | 103 |
| Prior radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 20 | 7 | 76 |
| No | 1 | 25 | 29 |
| Best response to last therapy | | | |
| According to the RECIST v.1.1, Complete Response: Disappearance of all target lesions; Partial Response: ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline; Progressive disease: ≥20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD | | | |
| Units: Subjects | | | |
| Complete response | 1 | 0 | 9 |
| Partial reponse | 2 | 5 | 70 |
| Stable disease | 6 | 14 | 19 |
| Progression disease | 7 | 11 | 4 |
| Unknown | 5 | 2 | 3 |
| Systemic lines | | | |
| Units: Subjects | | | |
| 1 line | 0 | 14 | 98 |
| 2 lines | 7 | 13 | 7 |
| 3 lines | 7 | 4 | 0 |
| 4 or more lines | 7 | 1 | 0 |
| Advanced chemotherapy lines | | | |
| 999, not applicable | | | |
| Units: Subjects | | | |
| 0 lines | 1 | 0 | 105 |
| 1 line | 5 | 17 | 0 |
| 2 lines | 7 | 10 | 0 |
| 3 lines | 6 | 4 | 0 |
| 4 or more lines | 2 | 1 | 0 |
| Weight | | | |
| Units: Kg | | | |
| median | 65.5 | 64.0 | 71.0 |
| full range (min-max) | 52.0 to 115.1 | 47.0 to 121.0 | 46.0 to 138.3 |

| | | | |
|---|-----------------------|---------------------|--------------------|
| Height Units: cm median full range (min-max) | 163.0 147 to 177 | 169 150 to 190 | 167 150 to 183 |
| Body surface area Units: m ² median full range (min-max) | 1.7 1.5 to 2.1 | 1.7 1.4 to 2.5 | 1.8 1.4 to 2.6 |
| Albumin Units: g/dL median full range (min-max) | 4.1 3.0 to 5.0 | 4.0 3.1 to 4.6 | 4.1 3.1 to 5.1 |
| Number of sites at baseline Units: Number of sites median full range (min-max) | 2 1 to 4 | 3 1 to 7 | 3 1 to 6 |
| Time from diagnosis to registration Units: months median full range (min-max) | 50.1 16.2 to 236.0 | 13.3 3.0 to 93.2 | 8.2 2.1 to 20.0 |
| Time from advanced disease to registration Units: month median full range (min-max) | 31.9 14.1 to 115.9 | 17.2 3.8 to 93.2 | 999 999 to 999 |
| Time to progression to last prior therapy Units: months median full range (min-max) | 5.0 1.3 to 32.1 | 3.6 1.1 to 24.0 | 6.5 1.4 to 17.8 |
| Time from last progression disease before study entry Units: weeks median full range (min-max) | 1.6 0.1 to 7.6 | 2.6 0.6 to 21.9 | 1.6 0.0 to 10.0 |

| | | | |
|--|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 335 | | |
| Age categorical Units: Subjects | | | |
| 18-40 years | 49 | | |
| 41-64 years | 173 | | |
| ≥65 years | 113 | | |
| Age continuous Units: years median full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 189 | | |
| Male | 146 | | |

| | | | |
|--|-----|--|--|
| Race | | | |
| Units: Subjects | | | |
| White | 242 | | |
| Not race available | 79 | | |
| Black of African American | 7 | | |
| Asian | 6 | | |
| American Indian or Alaska native | 1 | | |
| ECOG PS | | | |
| ECOG PS, Eastern Cooperative Oncology Group performance status. 0 Fully active, able to carry on all pre-disease performance without restriction 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature 2 Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours 3 Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours 4 Completely disabled; cannot carry on any selfcare; totally confined to bed or chair 5 Dead | | | |
| Units: Subjects | | | |
| PS 0 | 127 | | |
| PS 1 | 188 | | |
| PS 2 | 20 | | |
| Albumin | | | |
| Units: Subjects | | | |
| <3.5 g/dL | 50 | | |
| ≥3.5 g/dL | 285 | | |
| Stage at diagnosis | | | |
| Units: Subjects | | | |
| Early | 67 | | |
| Locally advanced | 87 | | |
| Metastatic | 181 | | |
| Sites at baseline | | | |
| Units: Subjects | | | |
| <3 sites | 144 | | |
| ≥3 sites | 191 | | |
| Prior surgery | | | |
| Units: Subjects | | | |
| Yes | 148 | | |
| No | 187 | | |
| Prior radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 190 | | |
| No | 145 | | |
| Best response to last therapy | | | |
| According to the RECIST v.1.1, Complete Response: Disappearance of all target lesions; Partial Response: ≥30% decrease in the sum of the longest diameters of target lesions compared with baseline; Progressive disease: ≥20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD | | | |
| Units: Subjects | | | |
| Complete response | 20 | | |
| Partial reponse | 112 | | |
| Stable disease | 71 | | |
| Progression disease | 71 | | |
| Unknown | 61 | | |

| | | | |
|---|-----|--|--|
| Systemic lines | | | |
| Units: Subjects | | | |
| 1 line | 201 | | |
| 2 lines | 82 | | |
| 3 lines | 29 | | |
| 4 or more lines | 23 | | |
| Advanced chemotherapy lines | | | |
| 999, not applicable | | | |
| Units: Subjects | | | |
| 0 lines | 145 | | |
| 1 line | 94 | | |
| 2 lines | 58 | | |
| 3 lines | 24 | | |
| 4 or more lines | 14 | | |
| Weight | | | |
| Units: Kg | | | |
| median | | | |
| full range (min-max) | - | | |
| Height | | | |
| Units: cm | | | |
| median | | | |
| full range (min-max) | - | | |
| Body surface area | | | |
| Units: m ² | | | |
| median | | | |
| full range (min-max) | - | | |
| Albumin | | | |
| Units: g/dL | | | |
| median | | | |
| full range (min-max) | - | | |
| Number of sites at baseline | | | |
| Units: Number of sites | | | |
| median | | | |
| full range (min-max) | - | | |
| Time from diagnosis to registration | | | |
| Units: months | | | |
| median | | | |
| full range (min-max) | - | | |
| Time from advanced disease to registration | | | |
| Units: month | | | |
| median | | | |
| full range (min-max) | - | | |
| Time to progression to last prior therapy | | | |
| Units: months | | | |
| median | | | |
| full range (min-max) | - | | |
| Time from last progression disease before study entry | | | |
| Units: weeks | | | |
| median | | | |
| full range (min-max) | - | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Biliary tract carcinoma cohort |
| Reporting group description: Patients with Pathologically proven diagnosis of biliary tract carcinoma | |
| Reporting group title | Carcinoma of unknown primary site cohort |
| Reporting group description: Patients with pathologically proven diagnosis of carcinoma of unknown primary site | |
| Reporting group title | Endometrial carcinoma cohort |
| Reporting group description: Patients with pathologically proven diagnosis of endometrial carcinoma | |
| Reporting group title | Ewing's Family of Tumors cohort |
| Reporting group description: Patients with pathologically proven diagnosis of Ewing's Family of Tumors | |
| Reporting group title | Germ Cell Tumors cohort |
| Reporting group description: Patients with pathologically proven diagnosis of Germ Cell Tumors, excluding immature teratoma, or teratoma with malignant transformation. | |
| Reporting group title | Head and Neck Carcinoma cohort |
| Reporting group description: Patients with Pathologically proven diagnosis of Head and Neck Carcinoma. Salivary glands tumors were excluded. | |
| Reporting group title | BRCA1/2-associated metastatic breast carcinoma cohort |
| Reporting group description: Patients with pathologically proven diagnosis of BRCA1/2-associated metastatic breast carcinoma | |
| Reporting group title | Neuroendocrine Tumors cohort |
| Reporting group description: Patients with Pathologically proven diagnosis of Neuroendocrine Tumors, grade 2 and 3 according to World Health Organization (WHO) classification. | |
| Reporting group title | Small Cell Lung Cancer cohort |
| Reporting group description: Patients with pathologically proven diagnosis of small cell lung cancer | |

Primary: Overall Response Rate by Investigator Assessment

| | |
|---|---|
| End point title | Overall Response Rate by Investigator Assessment ^[1] |
| End point description: Overall Response Rate was defined as the percentage of patients with a confirmed response, either CR or PR, according to the RECIST v.1.1. Complete Response: Disappearance of all target lesions; Partial Response: $\geq 30\%$ decrease in the sum of the longest diameters of target lesions compared with baseline; Progressive disease: $\geq 20\%$ increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD | |
| End point type | Primary |
| End point timeframe: From the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, until Cycle 6 (21-day cycle) | |

Notes:

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

Justification: The study is not a comparative design

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[2] | 19 | 71 ^[3] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 5.6 (0.1 to 27.3) | 0.0 (0.0 to 17.6) | 11.3 (5.0 to 21.0) | 14.3 (4.0 to 32.7) |

Notes:

[2] - 1 treatment discontinuation prior to have any disease measurement

[3] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[4] | 21 | 31 ^[5] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 4.3 (0.1 to 21.9) | 0.0 (0.0 to 24.7) | 28.6 (11.3 to 52.2) | 6.5 (0.8 to 21.4) |

Notes:

[4] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[5] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 35.2 (26.2 to 45.2) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Response by Investigator assessment

| | |
|-----------------|--|
| End point title | Response by Investigator assessment ^[6] |
|-----------------|--|

End point description:

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment deviations or if they are not evaluable. Each patient will be assigned one of the following:

Complete Response: Disappearance of all target lesions; Partial Response: $\geq 30\%$ decrease in the sum of the longest diameters of target lesions; Progressive disease: $\geq 20\%$ increase in the sum of the longest diameter of target lesions; diameter recorded or the appearance of one or more new lesions; Stable Disease: Neither PR or PD; Inevaluable for response: specify reasons (for example: early death, malignant disease, toxicity; tumour assessments not repeated/incomplete; other).

Normally, all eligible patients should be included in the denominator for the calculation of the response rate for phase II trials.

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

End point timeframe:

From the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, until Cycle 6 (21-day cycle)

Notes:

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

Justification: The study is not a comparative design

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|-----------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[7] | 19 | 71 ^[8] | 28 |
| Units: subjects | | | | |
| Complete Response | 0 | 0 | 2 | 0 |
| Partial Response | 1 | 0 | 6 | 4 |
| Stable Disease | 5 | 11 | 29 | 12 |
| Progressive disease | 11 | 7 | 30 | 9 |
| Inevaluable for response | 1 | 1 | 4 | 3 |

Notes:

[7] - 1 treatment discontinuation prior any measurement

[8] - 1 refusal prior first measurement

1 death (unrelated grade 5 septic shock)

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|-----------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[9] | 21 | 31 ^[10] |
| Units: subjects | | | | |
| Complete Response | 0 | 0 | 0 | 0 |
| Partial Response | 1 | 0 | 6 | 2 |
| Stable Disease | 8 | 3 | 10 | 9 |
| Progressive disease | 12 | 8 | 5 | 18 |
| Inevaluable for response | 2 | 2 | 0 | 2 |

Notes:

[9] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment.

[10] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|-----------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: subjects | | | | |
| Complete Response | 0 | | | |
| Partial Response | 37 | | | |
| Stable Disease | 35 | | | |
| Progressive disease | 28 | | | |
| Inevaluable for response | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of Response (DoR) by Investigator's Assessment (IA), defined as the time between the date when the response criteria (PR or CR, whichever one is first reached) are fulfilled to the first date when disease progression (PD), recurrence or death is documented.

0 and 999, not applicable (1 patient)

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

End point timeframe:

From the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, until Cycle 6 (21-day cycle)

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 ^[11] | 0 ^[12] | 8 ^[13] | 4 ^[14] |
| Units: months | | | | |
| median (confidence interval 95%) | 3.4 (0 to 999) | (to) | 9.2 (3.4 to 18.0) | 4.2 (2.9 to 5.5) |

Notes:

[11] - 1 of the 18 evaluable patients showed objective response to treatment

[12] - No patients with treatment response

[13] - Patients with response

[14] - 4 patients with response

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 ^[15] | 0 ^[16] | 6 ^[17] | 2 ^[18] |
| Units: months | | | | |
| median (confidence interval 95%) | 10.6 (0 to 999) | (to) | 8.6 (2.9 to 999) | 4.7 (4.0 to 5.4) |

Notes:

[15] - 1 Patient with response

[16] - No patients with response

[17] - 6 patients with response

[18] - 2 patients with response

| | | | | |
|----------------------------------|-------------------------------|--|--|--|
| End point values | Small Cell Lung Cancer cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 37 ^[19] | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.3 (4.1 to 6.4) | | | |

Notes:

[19] - Patients with response

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate

| | |
|---|-----------------------|
| End point title | Clinical Benefit Rate |
| End point description: | |
| Clinical Benefit Rate was defined as Overall Response Rate or Stable Disease lasting over four months (SD ≥ 4 months) | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, until Cycle 6 (21-day cycle) | |

| | | | | |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[20] | 19 | 71 ^[21] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 11.1 (1.4 to 34.7) | 36.8 (16.3 to 61.6) | 35.2 (24.2 to 47.5) | 39.3 (21.5 to 59.4) |

Notes:

[20] - 1 treatment discontinuation prior to have any disease measurement

[21] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| | | | | |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[22] | 21 | 31 ^[23] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 26.1 (10.2 to 48.4) | 15.4 (1.9 to 45.4) | 57.1 (34.0 to 78.2) | 29.0 (14.2 to 48.0) |

Notes:

[22] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[23] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 44.8 (35.0 to 54.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

| | |
|--|----------------------|
| End point title | Disease Control Rate |
| End point description: | |
| Disease Control Rate was defined as Overall Response Rate or Stable Disease | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of treatment to the date of progression or the start of a subsequent therapy or end of patient's follow-up, until Cycle 6 | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[24] | 19 | 71 ^[25] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 33.3 (13.3 to 59.0) | 57.9 (33.5 to 79.7) | 52.1 (39.9 to 64.1) | 57.1 (37.2 to 75.5) |

Notes:

[24] - 1 treatment discontinuation prior to have any disease measurement

[25] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[26] | 21 | 31 ^[27] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 39.1 (19.7 to 61.5) | 23.1 (5.0 to 53.8) | 76.2 (52.8 to 91.8) | 35.5 (19.2 to 54.6) |

Notes:

[26] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[27] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 68.6 (58.8 to 77.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

| | |
|---|---------------------------|
| End point title | Progression-free Survival |
| End point description: | |
| Progression-free Survival (PFS), defined as the period of time from the date of first infusion to the date of progression disease, death (of any cause), or last tumor evaluation | |
| Progressive disease: $\geq 20\%$ increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of first infusion to the date of progression disease, death (of any cause), or last tumor evaluation, up to an average of 5 years | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[28] | 19 | 71 ^[29] | 28 |
| Units: months | | | | |
| median (confidence interval 95%) | 1.3 (1.1 to 2.5) | 2.7 (1.3 to 4.4) | 2.6 (1.4 to 4.0) | 2.7 (1.4 to 4.3) |

Notes:

[28] - 1 treatment discontinuation prior to have any disease measurement

[29] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|-----------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[30] | 21 | 31 ^[31] |
| Units: months | | | | |

| | | | | |
|----------------------------------|------------------|------------------|------------------|------------------|
| median (confidence interval 95%) | 1.5 (0.9 to 8.9) | 1.3 (1.2 to 2.1) | 4.1 (2.3 to 6.5) | 1.4 (1.2 to 3.0) |
|----------------------------------|------------------|------------------|------------------|------------------|

Notes:

[30] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[31] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.5 (2.6 to 4.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival at 4 months

| | |
|--|---------------------------------------|
| End point title | Progression-free Survival at 4 months |
| End point description: | |
| Progression-free Survival at 4 (PFS4) by IA, defined as the probability of being free from progression and death after the first infusion at 4 months. | |
| End point type | Secondary |
| End point timeframe: | |
| At 4 months | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[32] | 19 | 71 ^[33] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 13.7 (0 to 31.1) | 38.9 (16.4 to 61.4) | 39.7 (28.2 to 51.3) | 46.2 (27.0 to 65.3) |

Notes:

[32] - 1 treatment discontinuation prior to have any disease measurement

[33] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[34] | 21 | 31 ^[35] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 30.7 (11.0 to 50.4) | 15.4 (0.0 to 35.0) | 57.1 (36.0 to 78.3) | 30.0 (13.6 to 46.4) |

Notes:

[34] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[35] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 46.6 (36.7 to 56.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival at 6 months

| | |
|--|---------------------------------------|
| End point title | Progression-free Survival at 6 months |
| End point description: | |
| Progression-free Survival at 6 (PFS6) by IA, defined as the probability of being free from progression and death after the first infusion at 6 months. | |
| End point type | Secondary |
| End point timeframe: | |
| At 6 months | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[36] | 19 | 71 ^[37] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 13.7 (0 to 31.1) | 22.2 (3.0 to 41.4) | 29.0 (18.2 to 39.8) | 23.1 (5.9 to 40.3) |

Notes:

[36] - 1 treatment discontinuation prior to have any disease measurement

[37] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[38] | 21 | 31 ^[39] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 30.7 (11.0 to 50.4) | 7.7 (0.0 to 22.2) | 33.3 (13.2 to 53.5) | 16.7 (3.3 to 30.0) |

Notes:

[38] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[39] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 32.9 (23.3 to 42.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

| | |
|--|------------------|
| End point title | Overall survival |
| End point description: | |
| Overall survival defined as the period of time from the date of first infusion to the date of death or last contact in case of patients lost to follow-up or alive at the clinical cutoff established for the cohort. 999, not reached | |
| End point type | Secondary |
| End point timeframe: | |
| From the date of first infusion to the date of death or last contact | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[40] | 19 | 71 ^[41] | 28 |
| Units: months | | | | |
| median (confidence interval 95%) | 7.3 (2.7 to 8.9) | 7.7 (3.8 to 18.8) | 9.3 (6.1 to 12.8) | 12.0 (8.5 to 18.5) |

Notes:

[40] - 1 treatment discontinuation prior to have any disease measurement

[41] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[42] | 21 | 31 ^[43] |
| Units: months | | | | |
| median (confidence interval 95%) | 9.2 (2.7 to 17.4) | 5.7 (2.1 to 12.1) | 16.1 (8.7 to 999) | 7.4 (3.4 to 16.2) |

Notes:

[42] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[43] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.3 (6.3 to 11.8) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 6 months

| | |
|---|------------------------------|
| End point title | Overall Survival at 6 months |
| End point description: | |
| Overall Survival at 6 months defined as the probability of being alive after the first infusion at 6 months | |
| End point type | Secondary |
| End point timeframe: | |
| At 6 months | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[44] | 19 | 71 ^[45] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 58.2 (34.5 to 82.0) | 55.6 (32.6 to 78.5) | 62.8 (51.2 to 74.4) | 88.2 (75.7 to 100.0) |

Notes:

[44] - 1 treatment discontinuation prior to have any disease measurement

[45] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[46] | 21 | 31 ^[47] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 55.0 (32.8 to 77.1) | 38.5 (12.0 to 64.9) | 79.2 (61.0 to 97.4) | 52.1 (33.9 to 70.3) |

Notes:

[46] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[47] - 1 patient refusal prior to have the first tumor assessment

| End point values | Small Cell Lung Cancer cohort | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 67.1 (57.6 to 76.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival at 12 months

| | |
|--|-------------------------------|
| End point title | Overall Survival at 12 months |
| End point description: Overall Survival at 12 months defined as the probability of being alive after the first infusion at 12 months. | |
| End point type | Secondary |
| End point timeframe: At 12 months | |

| End point values | Biliary tract carcinoma cohort | Carcinoma of unknown primary site cohort | Endometrial carcinoma cohort | Ewing's Family of Tumors cohort |
|----------------------------------|--------------------------------|--|------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 18 ^[48] | 19 | 71 ^[49] | 28 |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 21.8 (0.4 to 43.3) | 36.5 (13.1 to 59.8) | 45.8 (33.8 to 75.9) | 48.5 (27.8 to 69.2) |

Notes:

[48] - 1 treatment discontinuation prior to have any disease measurement

[49] - 1 refusal prior to the first disease measurement

1 death because unrelated grade 5 septic shock

| End point values | Germ Cell Tumors cohort | Head and Neck Carcinoma cohort | BRCA1/2-associated metastatic breast carcinoma cohort | Neuroendocrine Tumors cohort |
|----------------------------------|-------------------------|--------------------------------|---|------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 23 | 13 ^[50] | 21 | 31 ^[51] |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 34.4 (11.3 to 57.4) | 30.8 (5.7 to 55.9) | 58.1 (35.9 to 80.2) | 38.2 (20.5 to 55.9) |

Notes:

[50] - 1 patient's withdrawal and 1 unrelated grade 4 sepsis prior to the first assessment

[51] - 1 patient refusal prior to have the first tumor assessment

| | | | | |
|----------------------------------|-------------------------------|--|--|--|
| End point values | Small Cell Lung Cancer cohort | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 105 | | | |
| Units: percentage of patients | | | | |
| number (confidence interval 95%) | 34.2 (23.2 to 45.1) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of first infusion to the date of death or last contact, up to an average of 5 years

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Lurbinectedin |
|-----------------------|---------------|

Reporting group description:

Patients received lurbinectedin intravenously (i.v.) as a one-hour infusion on Day 1 q3wk (three weeks = one treatment cycle).

| Serious adverse events | Lurbinectedin | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 136 / 335 (40.60%) | | |
| number of deaths (all causes) | 261 | | |
| number of deaths resulting from adverse events | 18 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Embolism | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Superior vena cava occlusion | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior vena cava syndrome | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Cementoplasty | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 15 / 335 (4.48%) | | |
| occurrences causally related to treatment / all | 0 / 21 | | |
| deaths causally related to treatment / all | 0 / 8 | | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Oedema peripheral | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyrexia | | | | |
| subjects affected / exposed | 6 / 335 (1.79%) | | | |
| occurrences causally related to treatment / all | 2 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Acute respiratory failure | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aspiration | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Chronic obstructive pulmonary disease | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 8 / 335 (2.39%) | | | |
| occurrences causally related to treatment / all | 0 / 13 | | | |
| deaths causally related to treatment / all | 0 / 2 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

| | | | |
|---|-----------------|--|--|
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary arterial hypertension | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mental status changes | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Product issues | | | |
| Device malfunction | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood calcium decreased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood phosphorus decreased | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Platelet count decreased | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Compression fracture | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular access complication | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Facial paralysis | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hemiplegia | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neuralgia | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal cord compression | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Subacute combined cord degeneration | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 335 (2.99%) | | |
| occurrences causally related to treatment / all | 11 / 18 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 20 / 335 (5.97%) | | |
| occurrences causally related to treatment / all | 21 / 21 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 15 / 335 (4.48%) | | |
| occurrences causally related to treatment / all | 22 / 22 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 12 / 335 (3.58%) | | |
| occurrences causally related to treatment / all | 36 / 36 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |

| | | | | |
|---|------------------|--|--|--|
| Abdominal pain | | | | |
| subjects affected / exposed | 11 / 335 (3.28%) | | | |
| occurrences causally related to treatment / all | 0 / 12 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Colitis | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 1 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dysphagia | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intestinal obstruction | | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intra-abdominal haemorrhage | | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | | |
| occurrences causally related to treatment / all | 4 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Small intestinal obstruction | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 335 (2.09%) | | |
| occurrences causally related to treatment / all | 4 / 9 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaundice cholestatic | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 1 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Cushing's syndrome | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intervertebral disc compression | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|------------------------------------|--|--|
| Infections and infestations Bacteraemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 0 / 1 0 / 0 | | |
| Biliary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 0 / 1 0 / 0 | | |
| Bronchitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 0 / 1 0 / 0 | | |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 0 / 1 0 / 0 | | |
| Escherichia urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 1 / 1 0 / 0 | | |
| Lung infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 3 / 335 (0.90%) 1 / 3 1 / 1 | | |
| Peritonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 335 (0.30%) 0 / 1 0 / 0 | | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 8 / 335 (2.39%) 4 / 10 1 / 1 | | |
| Pseudomonal bacteraemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 335 (0.90%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Septic shock | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin infection | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 335 (0.30%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 335 (1.19%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 2 / 335 (0.60%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 7 / 335 (2.09%) | | |
| occurrences causally related to treatment / all | 3 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Lurbinectedin | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 330 / 335 (98.51%) | | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 25 / 335 (7.46%) | | |
| occurrences (all) | 33 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 28 / 335 (8.36%) | | |
| occurrences (all) | 34 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 25 / 335 (7.46%) | | |
| occurrences (all) | 28 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 19 / 335 (5.67%) | | |
| occurrences (all) | 27 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|--|--------------------|--|--|
| subjects affected / exposed | 59 / 335 (17.61%) | | |
| occurrences (all) | 100 | | |
| Neutropenia | | | |
| subjects affected / exposed | 89 / 335 (26.57%) | | |
| occurrences (all) | 174 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 129 / 335 (38.51%) | | |
| occurrences (all) | 335 | | |
| Chest pain | | | |
| subjects affected / exposed | 23 / 335 (6.87%) | | |
| occurrences (all) | 28 | | |
| Fatigue | | | |
| subjects affected / exposed | 122 / 335 (36.42%) | | |
| occurrences (all) | 242 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 19 / 335 (5.67%) | | |
| occurrences (all) | 23 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 30 / 335 (8.96%) | | |
| occurrences (all) | 35 | | |
| Pyrexia | | | |
| subjects affected / exposed | 48 / 335 (14.33%) | | |
| occurrences (all) | 56 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 54 / 335 (16.12%) | | |
| occurrences (all) | 83 | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 19 / 335 (5.67%) | | |
| occurrences (all) | 21 | | |
| Constipation | | | |
| subjects affected / exposed | 116 / 335 (34.63%) | | |
| occurrences (all) | 189 | | |
| Diarrhoea | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 62 / 335 (18.51%) | | |
| occurrences (all) | 104 | | |
| Nausea | | | |
| subjects affected / exposed | 167 / 335 (49.85%) | | |
| occurrences (all) | 276 | | |
| Vomiting | | | |
| subjects affected / exposed | 76 / 335 (22.69%) | | |
| occurrences (all) | 126 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 58 / 335 (17.31%) | | |
| occurrences (all) | 71 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 77 / 335 (22.99%) | | |
| occurrences (all) | 99 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 34 / 335 (10.15%) | | |
| occurrences (all) | 37 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 23 / 335 (6.87%) | | |
| occurrences (all) | 28 | | |
| Back pain | | | |
| subjects affected / exposed | 51 / 335 (15.22%) | | |
| occurrences (all) | 71 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 20 / 335 (5.97%) | | |
| occurrences (all) | 25 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 23 / 335 (6.87%) | | |
| occurrences (all) | 32 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 102 / 335 (30.45%) | | |
| occurrences (all) | 144 | | |

| | | | |
|--|------------------------|--|--|
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 18 / 335 (5.37%) 31 | | |
|--|------------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 13 May 2015 | <p>The main objective of this amendment was to update the lurbinectedin dose from 4.0 mg/m² to 3.2 mg/m² based on new data available. This reduction of the starting dose avoided dose adjustments in patients with ECOG PS=2 and/or aged > 70 years, and mandatory CSF prophylaxis was removed. This amendment was implemented previous to treat any patient; therefore, all patients included in this study were treated with lurbinectedin 3.2 mg/m².</p> <p>This amendment also included the following modifications in the protocol:</p> <ul style="list-style-type: none">• The timing of the assessment of AAGP levels was clarified by removing it from the Biochemistry B list of assessments and including it as a separate item in the Schedule of Assessments.• The timing of the blood sample collection for the PGt analysis was modified. The sample was then collected at any time during the study, but preferably just before treatment start in Cycle 1.• The primary prophylactic antiemetics that need to be administered to the patients and their routes were clarified.• Version 1.1 of RECIST was implemented in 2009 and was in common use ever since. Thus, the table describing the differences between RECIST 1.0 and 1.1 was no longer required and was removed.• Study dates and contact information were updated. |
| 04 February 2016 | <p>The following changes were implemented in this amendment:</p> <ul style="list-style-type: none">• An ongoing clinical trial with lurbinectedin as single agent in patients with BRCA1/2-associated metastatic breast cancer previously untreated with poly (ADP-ribose) polymerase (PARP) inhibitors was amended to include also patients who have received prior therapy with PARP inhibitors. Therefore, no more patients with this disease should be included in this phase II Basket study, and all information on breast cancer was removed.• Some eligibility criteria were revised:• The types of H&N and GCTs that could be included into the study were clarified.• The classification of NETs was updated according to Bosman, F.T. et al. WHO Classification of Tumours of the Digestive System (IARC Press, Lyon, France, 2010).• The prior treatment requirement for NETs and biliary tract carcinoma was changed to allow the inclusion of patients after one or two prior chemotherapy-containing lines.• MRI was added as a valid method for detecting brain metastases in SCLC patients at baseline.• Fertile patients who did not use an effective method of contraception were excluded from participation in the study.• The criteria for treatment continuation was made consistent with the protocol's eligibility criteria and the guidelines described in the Investigator's Brochure for lurbinectedin, following a request by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA). Re-treatment of patients with $\leq 1.5 \times$ ULN or creatinine clearance ≥ 30 mL/min was allowed.• Information on the statistical power of the study calculated using an exact binomial distribution was added.• The sample size of the cohort of SCLC patients in this study was to be increased to 50 evaluable patients if the success boundary (≥ 2 confirmed responses) was reached in the first 25 evaluable patients. This was done to collect further information on the efficacy and safety of single-agent lurbinectedin in this indication. |

| | |
|---------------|---|
| 22 March 2016 | <p>The protocol was amended to correct a typographic erratum in the inclusion criterion #10 describing the time when pregnancies must be avoided during the trial. In the previous substantial amendment #2, this time had already been changed from "six weeks after the last lurbinectedin administration" for all patients, to "three and four months after the last lurbinectedin administration for female patients and for partners of male patients, respectively" in other parts of the protocol. This amendment corrected this omission. Furthermore, a minor style edit change was also added (i.e., "men" instead of "male patients").</p> |
| 19 July 2016 | <p>The objective of this amendment was to allow up to 50 patients to be included in the endometrial carcinoma cohort of the study. Initially, up to 25 patients were planned per cohort to establish antitumor activity. In a previous amendment, the cohort of SCLC was increased to up to 50 patients (see Section 9.8.2). The current amendment allowed recruitment of up to 50 patients also in the endometrial carcinoma cohort. These two cohorts were expanded because of the antitumor activity already seen in a previous study of lurbinectedin in combination with doxorubicin (PM1183-A-003-10) and the need to confirm the activity of this compound as single agent in these indications. This change also affected the expected total number of patients.</p> <p>In response to Investigators' input and in order to broaden the eligible patient population in the EFT cohort, the prior treatment requirement (#4h) was also changed to "no more than two prior chemotherapy-containing lines in the metastatic/recurrent setting".</p> <p>The following changes, corrections, and clarifications were also included in this amendment:</p> <ul style="list-style-type: none"> • PK sample collection windows were extended in response to feedback from study centers and to facilitate compliance with study procedures. • Drug-drug interaction information was updated in line with current PK analysis and the current Investigator's Brochure (version 8.0, 10 March 2016). • In line with existing exclusion criterion #3, MRI was included as an option for baseline radiological tumor assessment in SCLC patients. • The criteria for treatment continuation included absence of active infection (including sepsis) and/or bleeding (any grade) in response to a requirement from the Belgian Competent Authority. • The definitions of 'Day 0' and associated assessment windows were clarified in order to ensure that patients had appropriate laboratory tests if first infusion was delayed. • Study contact details were updated. |
| 08 March 2017 | <p>The following changes were implemented in this amendment:</p> <ul style="list-style-type: none"> • To allow up to 100 patients to be included in the SCLC cohort. Due to the results in advanced SCLC observed in a prior clinical trial of lurbinectedin in combination with doxorubicin as a second line (response rate: 50%; 95%CI, 34– 66%), the cohort of SCLC was expanded to include 50 patients in a previous amendment. The rationale to further increase the patient population of this cohort to 100 patients was to confirm the activity of lurbinectedin as a single agent in patients with SCLC, which was found so far in the PM1183-B-005-14 trial, and to support the ongoing phase III clinical trial of lurbinectedin in combination with doxorubicin in advanced SCLC (PM1183-C-003-14). The statistical methods section was amended to update the sequential test methodology and to provide further details on the control of type I and II error probability (alpha and beta), taking into account the two planned interim analysis performed at 15 and 25 patients per group for the two expanded cohorts, endometrial carcinoma (50 patients) and SCLC (up to 100 patients added to the protocol). In addition, for all 100 patients in the SCLC cohort, anonymized copies of tumor assessments (CT-scan or MRI) were requested to the investigational sites for a possible independent review. These patients were to be followed up until death to obtain survival results (in this cohort, the secondary endpoint was changed to overall survival instead of one-year overall survival). • The cohort of patients with metastatic breast cancer (MBC) positive for the germline mutations BRCA1 and BRCA2 was re-opened. MBC with BRCA1/2 cohort was closed, due to redundancy with another ongoing clinical trial. The rationale for re-opening of the cohort was, first, the activity of lurbinectedin seen in the patient population of MBC BRCA+ already included in the study, leading to the request of patient inclusion by the Investigators participating in the trial. |

| | |
|--------------|--|
| 18 July 2018 | <ul style="list-style-type: none"> • Study objectives. Assessment of antitumor activity by an IRC was included as a secondary objective in the SCLC cohort. The inclusion of this secondary objective in the new version of the protocol led to changes throughout different sections of the protocol (e.g., statistical analysis, secondary endpoints, etc.). In addition, the SAP was also updated accordingly. The submission of anonymized copies of tumor assessments (CT-scan or MRI) from the investigational sites for a possible independent review was already implemented. These copies of CT scans, MRIs and any other documented methods to evaluate tumor response or progression in the SCLC cohort should be available for external radiological review by the IRC. • Patient population. The maximum number of evaluable patients was increased to 350 because of the elevated recruitment in the endometrial carcinoma cohort, which exceeded in 20 patients the planned number, together with the increase in the SCLC cohort to 100 evaluable patients, and the re-opening of the metastatic breast carcinoma BRCA-positive cohort, which had to recruit up to 25 patients. • Duration of recruitment period and total duration of the study. The duration of the recruitment period has been extended to approximately 40 months and the total duration of the study has been prolonged to 52 months. • Duration of follow-up period. The survival follow-up of the patients within each individual cohort, except those of the SCLC cohort, will be the following: after documentation of progressive disease (PD) or start of a new therapy, patients will be followed-up every six months until death or until the date of study termination or clinical cutoff (i.e., when all evaluable patients of each cohort, have at least 12 months of follow-up from the first PM01183 infusion). Patients in the SCLC cohort, after PD will be followed-up every six months until death. • Overall survival (OS). OS rate at 6 months and 12 months will be determined in each cohort. |
| 05 June 2020 | <p>The objective of this amendment was to change the clinical cutoff and duration of follow-up of patients treated with lurbinectedin in the SCLC cohort because of data for the primary endpoint (ORR) were considered mature at the time of this amendment.</p> <p>A previous amendment established that patients in the SCLC cohort were to be followed-up until death to assure the recording of survival results (in this cohort, the secondary endpoint was changed to overall survival instead of one-year overall survival). In the SCLC cohort, the first lurbinectedin dose in the first recruited patient was administered on 27 October 2015, and the first lurbinectedin dose in the last recruited patient was administered on 16 October 2018. Hence, by the end of July 2020, more than 18 months of follow-up could have been collected for all patients recruited in this cohort. Taking into account this information, median OS in the SCLC cohort could be considered steady and no changes in the point estimates were foreseen. Therefore, this amendment defined the duration of follow-up of patients in the SCLC cohort as at least 18 months from the first lurbinectedin infusion. The changes implemented in this amendment could not affect the results of the study.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported