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 Developtment, Department of PharmaMar´s Oncology, Business Unit., Pharmamar, S.A., 0034 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Developtment, 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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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/m^2. Dose was capped at body surface area (BSA) of 2.0 m^2 (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
Consent withdrawn by subject	-	1	5
Physician decision	-	1	2
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
Consent withdrawn by subject	2	3	2
Physician decision	1	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
Consent withdrawn by subject	-	1	2
Physician decision	-	1	4
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: ≥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	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	28.6	48.2	19.5
full range (min-max)	6.9 to 140.5	7.3 to 308.8	2.9 to 426.1
Time from advanced disease to registration			
Units: month			
median	20.4	999	18.4
full range (min-max)	0.4 to 54.2	999 to 999	9.7 to 72.7
Time to progression to last prior therapy			
Units: months			
median	8.7	2.7	4.6
full range (min-max)	0.4 to 25.8	0.8 to 29.6	1.4 to 26.1
Time from last progression disease before study entry			
Units: weeks			
median	2.1	1.4	2.4
full range (min-max)	0.0 to 7.1	0.3 to 6.4	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	45	63	60
full range (min-max)	29 to 73	23 to 77	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	163.0	169	167
full range (min-max)	147 to 177	150 to 190	150 to 183
Body surface area			
Units: m^2			
median	1.7	1.7	1.8
full range (min-max)	1.5 to 2.1	1.4 to 2.5	1.4 to 2.6
Albumin			
Units: g/dL			
median	4.1	4.0	4.1
full range (min-max)	3.0 to 5.0	3.1 to 4.6	3.1 to 5.1
Number of sites at baseline			
Units: Number of sites			
median	2	3	3
full range (min-max)	1 to 4	1 to 7	1 to 6
Time from diagnosis to registration			
Units: months			
median	50.1	13.3	8.2
full range (min-max)	16.2 to 236.0	3.0 to 93.2	2.1 to 20.0
Time from advanced disease to registration			
Units: month			
median	31.9	17.2	999
full range (min-max)	14.1 to 115.9	3.8 to 93.2	999 to 999
Time to progression to last prior therapy			
Units: months			
median	5.0	3.6	6.5
full range (min-max)	1.3 to 32.1	1.1 to 24.0	1.4 to 17.8
Time from last progression disease before study entry			
Units: weeks			
median	1.6	2.6	1.6
full range (min-max)	0.1 to 7.6	0.6 to 21.9	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: ≥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	
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: ≥30% decrease in the sum of the longest diameters of target lesions; Progressive disease: ≥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 patiens 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: ≥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 avergae 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	1 / 335 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biliary tract infection			
subjects affected / exposed	1 / 335 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 335 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 335 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary 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		
Lung infection			
subjects affected / exposed	3 / 335 (0.90%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Peritonitis			
subjects affected / exposed	1 / 335 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	8 / 335 (2.39%)		
occurrences causally related to treatment / all	4 / 10		
deaths causally related to treatment / all	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	The main objective of this amendment was to update the lurbinectedin dose from 4.0 mg/m^2 to 3.2 mg/m^2 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, andmandatory 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/m^2. This amendment also included the following modifications in the protocol: • 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	The following changes were implemented in this amendment: • 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 chemotherapycontaining 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 ≤ 1.5 x 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	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").
19 July 2016	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. 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". The following changes, corrections, and clarifications were also included in this amendment: • 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	The following changes were implemented in this amendment: • 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	• 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 thepatients 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	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. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported