Clinical trial results:
A Multicenter Phase II Clinical Trial of PM01183 in BRCA 1/2-Associated or Unselected Metastatic Breast Cancer.

Summary

EudraCT number	2011-006108-11
Trial protocol	ES
Global end of trial date	27 October 2018

Results information

Result version number	v1 (current)
This version publication date	18 July 2020
First version publication date	18 July 2020

Trial information

Trial identification

Sponsor protocol code	PM1183-B-003-11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01525589
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., Pharma Mar, S.A., 34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development Department of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., 34 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	03 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2018
Global end of trial reached?	Yes
Global end of trial date	27 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the antitumor activity of PM01183 in terms of overall response rate (ORR) according to RECIST vs 1.1 in each cohort of metastatic breast cancer (MBC) patients.

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 prophylactic medication at least 30 minutes before each administration of lurbinectedin, as follows:
• Corticosteroids (dexamethasone i.v. or equivalent at institutional standard antiemetic doses).
• Serotonin (5-HT3) antagonists (ondansetron 8 mg i.v. or equivalent).
If necessary and in addition to the above, any of the following could apply:
• Administration of 10 mg of metoclopramide (or equivalent) every eight hours.
• Extended treatment with 5-HT3 antagonists and/or dexamethasone.
Aprepitant and directly related agents (e.g., fosaprepitant) were forbidden.
For the purpose of safety evaluations, an optimal prophylaxis was defined as any of the aforementioned allowed medications at their respectively maximum dose.

Evidence for comparator: -

Actual start date of recruitment	13 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	United States: 60
Worldwide total number of subjects	111
EEA total number of subjects	51

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)	100
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was included on 27JUN12 and the first study treatment administration was on 28JUN12. The cutoff date for the results was 24OCT18.
A total of 111 patients were included in the 3 cohorts of the study: 56 in Cohort A (BRCA+), 20 in Cohort A1 (BRCA+/PARPi), 35 in Cohort B (Unselected).

Pre-assignment

Screening details:

Women 18-75 years;signed ICF;diagnosis of MBC;No more than three prior chemotherapy;ECOG PS 0-1;Adequate major organ function;Washout periods prior to D1 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	Cohort A (BRCA+)

Arm description:

Patients with known deleterious BRCA1/2 mutation status at study entry.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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 1h at a fixed infusion rate. Patients received lurbinectedin i.v. as a 1h infusion on D1 q3wk, at one of two starting doses:
- Patients included under protocol v1.0 v2.0 received lurbinectedin at a starting dose of 7.0 mg FD.
- Patients included from protocol v3.0 onwards received lurbinectedin at a starting dose of 3.5 mg/m2. Dose did not exceed 7.0 mg.
As a result, patients in Cohort A were treated at a starting dose of 7.0 mg FD or 3.5 mg/m2, and all patients in Cohort B were treated at a starting dose of 7.0 mg FD. Recruitment into Cohort A1 started after implementation of substantial amendment No. 3 (8MAR16); therefore, all patients in Cohort A1 were treated at a starting dose of 3.5 mg/m2.

Arm title	Cohort A1 (BRCA+/PARPi)

Arm description:

Patients with known deleterious BRCA1/2 mutation status and prior treatment with PARPi.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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 1h at a fixed infusion rate. Patients

received lurbinectedin i.v. as a 1h infusion on D1 q3wk, at one of two starting doses:
- Patients included under protocol v1.0 v2.0 received lurbinectedin at a starting dose of 7.0 mg FD.
- Patients included from protocol v3.0 onwards received lurbinectedin at a starting dose of 3.5 mg/m2. Dose did not exceed 7.0 mg.
As a result, patients in Cohort A were treated at a starting dose of 7.0 mg FD or 3.5 mg/m2, and all patients in Cohort B were treated at a starting dose of 7.0 mg FD. Recruitment into Cohort A1 started after implementation of substantial amendment No. 3 (8MAR16); therefore, all patients in Cohort A1 were treated at a starting dose of 3.5 mg/m2.

Arm title	Cohort B (Unselected)

Arm description:

Patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either:
- Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or
- Patients whose BRCA 1/2 mutation status was unknown (BRCA-UK). BRCA1/2 germline mutation status would be assessed in all patients in this subgroup responding to lurbinectedin treatment.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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 1h at a fixed infusion rate. Patients received lurbinectedin i.v. as a 1h infusion on D1 q3wk, at one of two starting doses:
- Patients included under protocol v1.0 v2.0 received lurbinectedin at a starting dose of 7.0 mg FD.
- Patients included from protocol v3.0 onwards received lurbinectedin at a starting dose of 3.5 mg/m2. Dose did not exceed 7.0 mg.
As a result, patients in Cohort A were treated at a starting dose of 7.0 mg FD or 3.5 mg/m2, and all patients in Cohort B were treated at a starting dose of 7.0 mg FD. Recruitment into Cohort A1 started after implementation of substantial amendment No. 3 (8MAR16); therefore, all patients in Cohort A1 were treated at a starting dose of 3.5 mg/m2.

Number of subjects in period 1	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)
Started	56	20	35
Completed	0	0	0
Not completed	56	20	35
Physician decision	4	2	2
Consent withdrawn by subject	-	1	-
Treatment-related AE	1	1	2
Non-treatment-related AE	1	-	-
Death (due to toxicity)	-	-	1
Other reasons	-	1	-
Never treated	2	-	-
Progressive disease	48	15	29
Death (non-treatment-related)	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (BRCA+)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status at study entry.	
Reporting group title	Cohort A1 (BRCA+/PARPi)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status and prior treatment with PARPi.	
Reporting group title	Cohort B (Unselected)
Reporting group description:	
Patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either: - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or - Patients whose BRCA 1/2 mutation status was unknown (BRCA-UK). BRCA1/2 germline mutation status would be assessed in all patients in this subgroup responding to lurbinectedin treatment.	

Reporting group values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)
Number of subjects	56	20	35
Age categorical Units: Subjects			
18-40	24	8	6
41-64	27	11	24
>=65	5	1	5
Age continuous Units: years			
median	42.5	45.0	52.0
full range (min-max)	30 to 73	31 to 66	32 to 70
Gender categorical Units: Subjects			
Female	56	20	35
Male	0	0	0
Race Units: Subjects			
Caucasian	50	16	32
Black	2	0	1
Asian	1	1	0
Hispanic	2	1	2
Unknown	1	2	0
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	32	10	22
PS 1	24	10	13
Sites of disease at diagnosis Units: Subjects			
Left breast	26	11	18
Right breast	28	9	15
Bilateral	2	0	2
Histology type at diagnosis			

Units: Subjects			
Ductal carcinoma	54	20	34
Lobular carcinoma	2	0	0
Lobular and ductal carcinoma	0	0	1
Histology grade at diagnosis			
Units: Subjects			
Well differentiated	3	0	1
Moderately differentiated	10	8	13
Poorly differentiated	31	11	17
Unknown	12	1	4
Stage at diagnosis			
Units: Subjects			
Stage I	9	3	0
Stage II	26	9	13
Stage III	16	6	19
Stage IV	5	2	3
BRCA deleterious mutation			
Units: Subjects			
BRCA1	33	10	0
BRCA2	23	9	0
Both	0	1	0
Not applicable	0	0	35
Hormonal status			
Units: Subjects			
Triple negative	33	7	17
ER and/or PR positive and HER2 negative	21	12	14
ER and/or PR positive and HER2 positive	2	1	3
ER and PR negative and HER2 positive	0	0	1
Sites at baseline			
Units: Subjects			
<3 sites	23	7	21
≥3 sites	33	13	14
Prior surgery			
Units: Subjects			
Yes	53	19	34
No	3	1	1
Prior radiotherapy			
Units: Subjects			
Yes	44	18	32
No	12	2	3
Weight			
Units: kg			
median	69.2	59.8	71.7
full range (min-max)	48.4 to 107.3	48.5 to 98.8	43.0 to 153.6
Height			
Units: cm			
median	162.5	161.0	161.0
full range (min-max)	150.0 to 178.0	148.0 to 173.0	147.0 to 171.0
BSA			

BSA, body surface area			
Units: m2			
median	1.72	1.63	1.75
full range (min-max)	1.47 to 2.12	1.48 to 2.05	1.36 to 2.41
Albumin			
Units: g/dL			
median	4.1	4.1	4.0
full range (min-max)	3.3 to 4.9	3.6 to 4.8	3.4 to 4.6
Number of sites at baseline			
Units: Number of sites			
median	3.0	3.0	2.0
full range (min-max)	1 to 7	1 to 6	1 to 6
Time from first diagnosis to registration			
Units: months			
median	44.0	55.7	47.0
full range (min-max)	0.9 to 170.3	11.5 to 337.3	5.0 to 177.3
Time from metastatic disease to registration			
Units: months			
median	12.5	26.1	13.8
full range (min-max)	0.4 to 129.8	8.4 to 98.2	2.5 to 110.9
Time from last progression before study entry			
Units: weeks			
median	2.9	3.2	3.0
full range (min-max)	0.0 to 15.6	0.9 to 14.0	0.7 to 8.1

Reporting group values	Total		
Number of subjects	111		
Age categorical			
Units: Subjects			
18-40	38		
41-64	62		
>=65	11		
Age continuous			
Units: years			
median			
full range (min-max)	-		
Gender categorical			
Units: Subjects			
Female	111		
Male	0		
Race			
Units: Subjects			
Caucasian	98		
Black	3		
Asian	2		
Hispanic	5		
Unknown	3		
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			

PS 0	64		
PS 1	47		
Sites of disease at diagnosis Units: Subjects			
Left breast	55		
Right breast	52		
Bilateral	4		
Histology type at diagnosis Units: Subjects			
Ductal carcinoma	108		
Lobular carcinoma	2		
Lobular and ductal carcinoma	1		
Histology grade at diagnosis Units: Subjects			
Well differentiated	4		
Moderately differentiated	31		
Poorly differentiated	59		
Unknown	17		
Stage at diagnosis Units: Subjects			
Stage I	12		
Stage II	48		
Stage III	41		
Stage IV	10		
BRCA deleterious mutation Units: Subjects			
BRCA1	43		
BRCA2	32		
Both	1		
Not applicable	35		
Hormonal status Units: Subjects			
Triple negative	57		
ER and/or PR positive and HER2 negative	47		
ER and/or PR positive and HER2 positive	6		
ER and PR negative and HER2 positive	1		
Sites at baseline Units: Subjects			
<3 sites	51		
≥3 sites	60		
Prior surgery Units: Subjects			
Yes	106		
No	5		
Prior radiotherapy Units: Subjects			
Yes	94		
No	17		

Weight Units: kg median full range (min-max)	-		
Height Units: cm median full range (min-max)	-		
BSA			
BSA, body surface area			
Units: m2 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 first diagnosis to registration Units: months median full range (min-max)	-		
Time from metastatic disease to registration Units: months median full range (min-max)	-		
Time from last progression before study entry Units: weeks median full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Cohort A (BRCA+)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status at study entry.	
Reporting group title	Cohort A1 (BRCA+/PARPi)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status and prior treatment with PARPi.	
Reporting group title	Cohort B (Unselected)
Reporting group description:	
Patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either: - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or - Patients whose BRCA 1/2 mutation status was unknown (BRCA-UK). BRCA1/2 germline mutation status would be assessed in all patients in this subgroup responding to lurbinectedin treatment.	

Primary: Overall Response Rate

End point title	Overall Response Rate[1]
End point description:	
Overall Response Rate (ORR) in the population evaluable for efficacy according to RECIST v.1.1. ORR was defined as the percentage of patients with a confirmed response, either CR or PR, according to the RECIST v.1.1.	
End point type	Primary
End point timeframe:	
Overall period	

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: No comparative design. Multicenter, open-label, exploratory, phase II clinical trial to evaluate the efficacy and safety of lurbinectedin in previously treated patients with MBC. Three cohorts of MBC patients were prospectively evaluated.

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[2]	20	34[3]	
Units: percent				
median (confidence interval 95%)	40.7 (27.6 to 55.0)	5.0 (0.1 to 24.9)	8.8 (1.9 to 23.7)	

Notes:

[2] - Two patients never treated

[3] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

No statistical analyses for this end point

Primary: Overall Response

End point title	Overall Response[4]
End point description:	
Overall Response Rate (ORR) in the population evaluable for efficacy according to RECIST v.1.1. ORR was defined as the percentage of patients with a confirmed response, either CR or PR, according to the	

RECIST v.1.1.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; TF, treatment failure

End point type	Primary

End point timeframe:

Overall period

Notes:

[4] - 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: No comparative design. Multicenter, open-label, exploratory, phase II clinical trial to evaluate the efficacy and safety of lurbinectedin in previously treated patients with MBC. Three cohorts of MBC patients were prospectively evaluated.

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[5]	20	34[6]	
Units: subjects				
CR	2	0	0	
PR	20	1	3	
SD	24	9	17	
PD	8	10	13	
TF	0	0	1	

Notes:

[5] - 2 patients never treated

[6] - 1 patient due to lack of post-baseline tumor assessments

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), defined as the time between the date when the response criteria (PR or CR, whichever was first reached) were fulfilled to the first date when disease progression (PD), recurrence or death was documented.
000, 999: not reached

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[7]	1[8]	3[9]	
Units: months				
median (confidence interval 95%)	6.3 (3.4 to 12.7)	2.7 (000 to 999)	3.6 (2.1 to 16.1)	

Notes:

[7] - 22 responder patients

[8] - 1 responder patients

[9] - 3 responder patients

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Cohort A (BRCA+) v Cohort A1 (BRCA+/PARPi) v Cohort B (Unselected)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0909
Method	Logrank

Secondary: Duration of response rate at 6 months

End point title	Duration of response rate at 6 months

End point description:

Duration of response (DoR), defined as the time between the date when the response criteria (PR or CR, whichever was first reached) were fulfilled to the first date when disease progression (PD), recurrence or death was documented.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[10]	1[11]	3[12]	
Units: percent				
number (confidence interval 95%)	53.1 (31.8 to 74.4)	0 (0 to 999)	33.3 (0 to 86.7)	

Notes:

[10] - 22 responder patients

[11] - 1 responder patients

[12] - 3 responder patients

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response rate at 12 months

End point title	Duration of response rate at 12 months

End point description:

Duration of response (DoR), defined as the time between the date when the response criteria (PR or CR, whichever was first reached) were fulfilled to the first date when disease progression (PD), recurrence or

death was documented.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[13]	1[14]	3[15]	
Units: percent				
number (confidence interval 95%)	33.8 (13.5 to 54.1)	0 (0 to 999)	33.3 (0 to 86.7)	

Notes:

[13] - 22 responder patients

[14] - 1 responder patients

[15] - 3 responder patients

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate

End point title	Clinical benefit rate

End point description:

Clinical benefit, defined as the percentage of patients with ORR or SD lasting over three months (SD >3 months).

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[16]	20	34[17]	
Units: percent				
number (confidence interval 95%)	61.1 (46.9 to 74.1)	40.0 (19.1 to 63.9)	32.4 (17.4 to 50.5)	

Notes:

[16] - 2 patients never treated

[17] - 1 patient due to lack of post-baseline tumor assessments

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 PD, death (due to any cause), or last tumor evaluation	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[18]	20	34[19]	
Units: months				
median (confidence interval 95%)	4.6 (3.0 to 6.2)	1.4 (1.3 to 3.9)	2.5 (1.3 to 3.4)	

Notes:

[18] - 2 patients never treated

[19] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Cohort A1 (BRCA+/PARPi) v Cohort B (Unselected) v Cohort A (BRCA+)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Logrank

Secondary: Progression-free survival at 3 months

End point title	Progression-free survival at 3 months
End point description:	
Progression-free survival (PFS), defined as the period of time from the date of first infusion to the date of PD, death (due to any cause), or last tumor evaluation	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[20]	20	34[21]	
Units: percent				
number (confidence interval 95%)	63.5 (50.4 to 76.6)	42.5 (20.3 to 64.7)	35.5 (18.9 to 52.1)	

Notes:

[20] - 2 patients never treated

[21] - 1 patient due to lack of post-baseline tumor assessments

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 (PFS), defined as the period of time from the date of first infusion to the date of PD, death (due to any cause), or last tumor evaluation.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[22]	20	34[23]	
Units: percent				
number (confidence interval 95%)	37.6 (24.2 to 50.9)	21.3 (2.8 to 39.7)	11.1 (0 to 22.6)	

Notes:

[22] - 2 patients never treated

[23] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival at 12 months

End point title	Progression-free survival at 12 months

End point description:

Progression-free survival (PFS), defined as the period of time from the date of first infusion to the date of PD, death (due to any cause), or last tumor evaluation.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[24]	20	34[25]	
Units: percent				
number (confidence interval 95%)	20.5 (9.1 to 31.9)	0 (0 to 0)	3.7 (0 to 10.7)	

Notes:

[24] - 2 patients never treated

[25] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS), defined as the time from the date of first infusion to the date of death or last contact

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[26]	20	34[27]	
Units: months				
median (confidence interval 95%)	18.6 (10.9 to 22.8)	8.1 (4.6 to 14.6)	12.1 (6.6 to 17.9)	

Notes:

[26] - 2 patients never treated

[27] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

Statistical analysis title	Differences between groups
Comparison groups	Cohort A (BRCA+) v Cohort A1 (BRCA+/PARPi) v Cohort B (Unselected)
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0561
Method	Logrank

Secondary: Overall survival rate at 12 months

End point title	Overall survival rate at 12 months

End point description:

Overall survival (OS), defined as the time from the date of first infusion to the date of death or last contact.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[28]	20	34[29]	
Units: percent				
number (confidence interval 95%)	62.5 (49.0 to 75.9)	29.7 (7.9 to 51.5)	55.4 (37.9 to 73.0)	

Notes:

[28] - 2 patients never treated

[29] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival rate at 18 months

End point title	Overall survival rate at 18 months

End point description:

Overall survival (OS), defined as the time from the date of first infusion to the date of death or last contact.

End point type	Secondary

End point timeframe:

Overall period

End point values	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54[30]	20	34[31]	
Units: percent				
number (confidence interval 95%)	53.4 (39.2 to 67.5)	22.3 (1.6 to 42.9)	27.7 (11.5 to 43.9)	

Notes:

[30] - 2 patients never treated

[31] - 1 patient due to lack of post-baseline tumor assessments

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	Cohort A (BRCA+)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status at study entry.	
Reporting group title	Cohort A1 (BRCA+/PARPi)
Reporting group description:	
Patients with known deleterious BRCA1/2 mutation status and prior treatment with PARPi.	
Reporting group title	Cohort B (Unselected)
Reporting group description:	
Patients without known deleterious BRCA1/2 mutation status at study entry, i.e., either: - Patients known to have no deleterious BRCA1/2 mutations (BRCA−), or - Patients whose BRCA 1/2 mutation status was unknown (BRCA-UK). BRCA1/2 germline mutation status would be assessed in all patients in this subgroup responding to lurbinectedin treatment.	

Serious adverse events	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 54 (25.93%)	5 / 20 (25.00%)	8 / 35 (22.86%)
number of deaths (all causes)	40	13	30
number of deaths resulting from adverse events	1	0	2
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Catheter site erythema			

subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug interaction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Neutropenia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	7 / 54 (12.96%)	2 / 20 (10.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	9 / 9	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	6 / 54 (11.11%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	9 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Myelitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Staphylococcal bacteraemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Listeriosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort A (BRCA+)	Cohort A1 (BRCA+/PARPi)	Cohort B (Unselected)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 54 (100.00%)	20 / 20 (100.00%)	34 / 35 (97.14%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Hot flush			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	2	0
Hypotension			

subjects affected / exposed	1 / 54 (1.85%)	2 / 20 (10.00%)	2 / 35 (5.71%)
occurrences (all)	1	2	2
Lymphoedema			
subjects affected / exposed	4 / 54 (7.41%)	0 / 20 (0.00%)	4 / 35 (11.43%)
occurrences (all)	5	0	5
Phlebitis			
subjects affected / exposed	4 / 54 (7.41%)	2 / 20 (10.00%)	2 / 35 (5.71%)
occurrences (all)	5	3	2
Flushing			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	1 / 54 (1.85%)	2 / 20 (10.00%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Fatigue			
subjects affected / exposed	48 / 54 (88.89%)	10 / 20 (50.00%)	30 / 35 (85.71%)
occurrences (all)	195	21	66
Gait disturbance			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	3	0	2
Influenza like illness			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	4	0	1
Infusion site pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Mucosal inflammation			
subjects affected / exposed	13 / 54 (24.07%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	15	1	2
Non-cardiac chest pain			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	2	4	0
Oedema			

subjects affected / exposed	5 / 54 (9.26%)	2 / 20 (10.00%)	4 / 35 (11.43%)
occurrences (all)	13	2	5
Pain			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	4	0	1
Pyrexia			
subjects affected / exposed	8 / 54 (14.81%)	4 / 20 (20.00%)	6 / 35 (17.14%)
occurrences (all)	10	5	16
Chest discomfort			
subjects affected / exposed	0 / 54 (0.00%)	2 / 20 (10.00%)	0 / 35 (0.00%)
occurrences (all)	0	3	0
Localised oedema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Pelvic pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 54 (29.63%)	2 / 20 (10.00%)	6 / 35 (17.14%)
occurrences (all)	21	2	9
Dyspnoea			
subjects affected / exposed	11 / 54 (20.37%)	5 / 20 (25.00%)	8 / 35 (22.86%)
occurrences (all)	12	11	12
Nasal congestion			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Oropharyngeal pain			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Pleural effusion			

subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Pulmonary embolism			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	8 / 54 (14.81%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	9	0	2
Depression			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	3	0	2
Insomnia			
subjects affected / exposed	4 / 54 (7.41%)	2 / 20 (10.00%)	1 / 35 (2.86%)
occurrences (all)	4	2	1
Investigations			
Neutropenia			
subjects affected / exposed	24 / 54 (44.44%)	11 / 20 (55.00%)	7 / 35 (20.00%)
occurrences (all)	48	15	9
Alanine aminotransferase			
subjects affected / exposed	3 / 54 (5.56%)	2 / 20 (10.00%)	1 / 35 (2.86%)
occurrences (all)	3	5	1
Aspartate aminotransferase			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Breath sounds abnormal			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	0 / 54 (0.00%)	2 / 20 (10.00%)	2 / 35 (5.71%)
occurrences (all)	0	2	2
Platelet count decreased			

subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
fall			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	2	1	0
Lower limb fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	5 / 54 (9.26%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	8	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 54 (12.96%)	2 / 20 (10.00%)	3 / 35 (8.57%)
occurrences (all)	9	3	4
Dysgeusia			
subjects affected / exposed	3 / 54 (5.56%)	2 / 20 (10.00%)	0 / 35 (0.00%)
occurrences (all)	8	2	0
Headache			
subjects affected / exposed	16 / 54 (29.63%)	6 / 20 (30.00%)	5 / 35 (14.29%)
occurrences (all)	29	10	5
Neuralgia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Neuropathy peripheral			
subjects affected / exposed	6 / 54 (11.11%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	6	1	2
Tremor			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	13 / 54 (24.07%)	2 / 20 (10.00%)	6 / 35 (17.14%)
occurrences (all)	16	3	10
Febrile neutropenia			
subjects affected / exposed	4 / 54 (7.41%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences (all)	4	0	0
Neutropenia			
subjects affected / exposed	24 / 54 (44.44%)	11 / 20 (55.00%)	7 / 35 (20.00%)
occurrences (all)	48	15	9
Thrombocytopenia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	11 / 54 (20.37%)	5 / 20 (25.00%)	7 / 35 (20.00%)
occurrences (all)	25	6	12
Constipation			
subjects affected / exposed	23 / 54 (42.59%)	9 / 20 (45.00%)	9 / 35 (25.71%)
occurrences (all)	32	17	17
Diarrhoea			
subjects affected / exposed	16 / 54 (29.63%)	4 / 20 (20.00%)	5 / 35 (14.29%)
occurrences (all)	23	7	6
Dyspepsia			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	3	1	3
Nausea			
subjects affected / exposed	43 / 54 (79.63%)	15 / 20 (75.00%)	20 / 35 (57.14%)
occurrences (all)	123	23	37
Odynophagia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Vomiting			

subjects affected / exposed	23 / 54 (42.59%)	7 / 20 (35.00%)	10 / 35 (28.57%)
occurrences (all)	48	9	13
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Hepatomegaly			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	3 / 35 (8.57%)
occurrences (all)	0	0	3
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Dry skin			
subjects affected / exposed	4 / 54 (7.41%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	4	0	2
Erythema			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
Pruritus			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Rash			
subjects affected / exposed	8 / 54 (14.81%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	10	1	2
Skin hyperpigmentation			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	2	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 54 (1.85%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	1	0	2
Pollakiuria			

subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			
Cushingoid			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 54 (7.41%)	4 / 20 (20.00%)	3 / 35 (8.57%)
occurrences (all)	6	6	3
Back pain			
subjects affected / exposed	7 / 54 (12.96%)	2 / 20 (10.00%)	4 / 35 (11.43%)
occurrences (all)	9	5	5
Bone pain			
subjects affected / exposed	8 / 54 (14.81%)	2 / 20 (10.00%)	2 / 35 (5.71%)
occurrences (all)	10	2	2
Musculoskeletal discomfort			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
Myalgia			
subjects affected / exposed	5 / 54 (9.26%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	9	0	1
Neck pain			
subjects affected / exposed	2 / 54 (3.70%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	2	0	2
Pain in extremity			
subjects affected / exposed	6 / 54 (11.11%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	8	0	2
Pain in jaw			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	1	2	1
Musculoskeletal pain			
subjects affected / exposed	9 / 54 (16.67%)	2 / 20 (10.00%)	4 / 35 (11.43%)
occurrences (all)	10	2	5
Infections and infestations			

Bronchitis			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	1 / 35 (2.86%)
occurrences (all)	3	0	1
Herpes zoster			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	4 / 54 (7.41%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	5	2	1
Pharyngitis			
subjects affected / exposed	3 / 54 (5.56%)	0 / 20 (0.00%)	0 / 35 (0.00%)
occurrences (all)	3	0	0
Sinusitis			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	2 / 54 (3.70%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	2	1	2
Urinary tract infection			
subjects affected / exposed	6 / 54 (11.11%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	9	1	1
Candidiasis of trachea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Klebsiella infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	1	0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	0	2	0
Sputum purulent			
subjects affected / exposed	0 / 54 (0.00%)	0 / 20 (0.00%)	2 / 35 (5.71%)
occurrences (all)	0	0	5
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	15 / 54 (27.78%)	6 / 20 (30.00%)	5 / 35 (14.29%)
occurrences (all)	20	7	9
Dehydration			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	1	1	1
Hypokalaemia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	0 / 35 (0.00%)
occurrences (all)	3	3	0
Hypomagnesaemia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 20 (5.00%)	2 / 35 (5.71%)
occurrences (all)	1	1	2
Hyponatraemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 20 (5.00%)	1 / 35 (2.86%)
occurrences (all)	0	1	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 December 2013	The following changes were implemented in this amendment: • The BRCA mutation assessment was added to the screening procedures for those candidates to be enrolled into the trial whose BRCA status was unknown and there was high suspicion of being BRCA-mutated. This was done in accordance with the National Comprehensive Cancer Network (NCCN) criteria for consideration of BRCA1/2 genetic testing. • The frequency of hematological tests in the event of febrile neutropenia of any grade, grade 4 neutropenia and/or grade 4 thrombocytopenia was changed, so that they had to be conducted at least every 48-72 hours until recovery to at least grade 2. • A statement was added to clarify that the Sponsor could request the study sites to provide the imaging tests conducted on the patients during the clinical trial, for evaluation. • Information on the laboratories for PGx analyses was updated, and a statement was added to clarify that polymorphisms and mutational status of genes involved in DNA repair mechanisms, or related to the mechanism of action of lurbinectedin or to the disease, could also be analyzed if relevant. • Information on the laboratory responsible for the BRCA1/2 mutation analysis was added. • A typographic mistake was corrected.
28 October 2014	The following changes were implemented: • Lurbinectedin dosing was modified from a fixed dose to a BSA-based dose. This conservative approach was adopted following a logistic regression analysis of data from the first 64 patients enrolled in this trial, which found a statistically significant relationship between BSA and the possibility of developing grade 3/4 neutropenia while on treatment with lurbinectedin at 7.0 mg FD on Day 1 q3wk. Patients with lower BSA values were found to be at highest risk. This dose adjustment was expected to reduce the incidence of grade 3/4 neutropenia, which at the time was the most common lurbinectedin toxicity observed so far. • Some eligibility criteria were revised: - The prior requirement that BRCA+ MBC patients had to have received at least one prior chemotherapy-containing line for advanced disease to be included in the study was removed. - The prior requirement that patients liver metastases had to have ALT and AST values ≤5.0 x ULN to be included in the study was removed. - Patients previously treated with PARPi were no longer allowed to be included in the study. - A clarification was added to allow the inclusion of patients with in situ melanoma. • A clarification was added to specify that use of aprepitant and directly related compounds (e.g., fosaprepitant) was forbidden. • Primary G-CSF prophylaxis remained limited but could be permitted on a caseby-case basis. • The planned study duration was updated to include a longer enrolment period to reflect recruitment rates at the time. • The follow-up period and the schedule after end of treatment were clarified. • Safety reporting contact details were updated. • Preclinical information about lurbinectedin drug-drug interactions was updated. • Appendix 4, which listed commonly used medications known to be CYP2C8- and CYP3A4-substrates, was replaced with a list of CYP1/CYP2/CYP3 inhibitors, inducers and substrates. • New version of the WMA Declaration of Helsinki

08 March 2016	The following changes were implemented in this amendment: • A new cohort (Cohort A1) was implemented to evaluate lurbinectedin specifically in BRCA+ MBC patients previously treated with PARPi. These patients had been excluded from this study following the implementation of substantial amendment No. 2 (see Section 9.8.2). However, this decision was reverted owing to the increasing relevance of PARPi in the treatment of MBC. Evaluation of more BRCA+ MBC patients previously treated with PARPi was further justified to determine if tumor cell resistance mechanisms might affect the antitumor activity of lurbinectedin, and to establish if the ORR difference observed in Cohort A between patients previously treated or not with PARPi might be explained by other variables (e.g., number of prior treatment lines, best response to last treatment or to PARPi, patient characteristics, etc.). • The PGx substudy was amended to make it mandatory for patients included in the new cohort (it had been optional for patients in Cohorts A and B). Hence, patients in Cohort A1 were asked to undergo a tumor biopsy at study entry to evaluate potential biomarkers of resistance/sensitivity to lurbinectedin after PARPi administration. This was in addition to the archived diagnostic sample (if available). • The planned study duration was updated to include a longer enrollment period. • References to R1 of the ICH Topic E6 Guideline for Good Clinical Practice were removed, in anticipation of a new revised version of the document. • Study contact information was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: