Clinical trial results:
Phase III Randomized Clinical Trial of Lurbinectedin (PM01183) /Doxorubicin (DOX) versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial)

Summary

EudraCT number	2015-001641-89
Trial protocol	HU AT BE ES DE GR PT CZ NL BG GB PL IT
Global end of trial date	24 February 2020

Results information

Result version number	v1 (current)
This version publication date	15 August 2021
First version publication date	15 August 2021

Trial information

Trial identification

Sponsor protocol code	PM1183-C-003-14

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02566993
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-Norte Colmenar Viejo, Spain, 28770
Public contact	Clinical Trials, Pharma Mar, S.A., +34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Trials, 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	24 February 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to determine a difference in overall survival (OS) between Lurbinectedin/DOX (Experimental Arm) and Topotecan or Cyclophosphamide, Doxorubicin and Vincristine (Control Arm) in SCLC subjects after failure of one prior platinum-containing line.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2016
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	Canada: 17
Country: Number of subjects enrolled	Brazil: 28
Country: Number of subjects enrolled	Argentina: 7
Country: Number of subjects enrolled	Lebanon: 17
Country: Number of subjects enrolled	United States: 62
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 67
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Hungary: 46
Country: Number of subjects enrolled	Italy: 41
Country: Number of subjects enrolled	Netherlands: 18
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Spain: 125
Country: Number of subjects enrolled	Czechia: 9

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	613
EEA total number of subjects	461

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	356
From 65 to 84 years	257
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 919 subjects were screened at 135 sites in 20 countries, of whom 613 subjects were randomized to receive the study treatments.

Pre-assignment

Screening details:

Subjects who met the eligibility criteria were randomized in a 1:1 ratio to receive either Lurbinectedin (PM01183)/Doxorubicin or Cyclophosphamide/Doxorubicin/Vincristine (CAV) or Topotecan.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lurbinectedin + Doxorubicin

Arm description:

Subjects received intravenous (IV) infusion of Doxorubicin at a dose of 40.0 milligrams per meter square (mg/m^2) on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m^2 over one hour on Day 1 every three weeks (q3wk) up to ten cycles. Then, if applicable, Doxorubicin was discontinued and the subjects received maintenance treatment along with Lurbinectedin alone intravenously on Day 1 q3wk at a dose of 3.2 mg/m^2 (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m^2 (if more than one dose reduction applied while on combination therapy) until progressive disease (PD), subject refusal or unacceptable toxicity despite applicable dose reductions.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	PM01183
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Lurbinectedin on Day 1 q3wk.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Doxorubicin on Day 1 q3wk.

Arm title	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Arm description:

Subjects received either IV infusion of Topotecan at a dose of 1.50 mg/m^2 for subjects with calculated creatinine clearance (CrCL) more than or equal to (>=) 60 milliliter per minutes (mL/min); 1.25 mg/m^2 for subjects with CrCL between 40 and 59 mL/min; 0.75 mg/m2 for subjects with CrCL between 30 and 39 mL/min on Days 1 to5 q3wk or IV infusion Cyclophosphamide (CTX) 1000 mg/m^2 in combination with IV infusion of Doxorubicin (DOX) at a dose of 45.0 mg/m^2 and Vincristine (VCR) at a dose of 2.0 (mg) flat dose (FD) on Day 1 q3wk for up to ten cycles. Then, if applicable, DOX was discontinued and the subjects received maintenance treatment until PD, subject's refusal or unacceptable toxicity despite applicable dose reductions.

Arm type	Active comparator

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Cyclophosphamide on Day 1 q3wk.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Doxorubicin on Day 1 q3wk.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Vincristine on Day 1 q3wk.

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received IV infusion of Topotecan on Days 1-to 5 q3wk.

Number of subjects in period 1	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Started	307	306
Safety Set	303	289
Completed	0	1
Not completed	307	305
Physician decision	10	17
Study drug-related adverse event (AE)	20	41
Incorrect assessment of pharmacodynamic	1	-
Consent withdrawn by subject	12	28
Study termination	9	1
Symptomatic deterioration	9	16
Death	17	23
Progressive Disease	213	152

Non study drug-related AE	9	9
Sponsor's decision after incorrect treatment	2	-
Not meeting eligibility criteria	1	-
Randomised, not treated	4	16
Lost to follow-up	-	1
Symptomatic deterioration and physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Lurbinectedin + Doxorubicin

Reporting group description:

Subjects received intravenous (IV) infusion of Doxorubicin at a dose of 40.0 milligrams per meter square (mg/m^2) on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m^2 over one hour on Day 1 every three weeks (q3wk) up to ten cycles. Then, if applicable, Doxorubicin was discontinued and the subjects received maintenance treatment along with Lurbinectedin alone intravenously on Day 1 q3wk at a dose of 3.2 mg/m^2 (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m^2 (if more than one dose reduction applied while on combination therapy) until progressive disease (PD), subject refusal or unacceptable toxicity despite applicable dose reductions.

Reporting group title	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Reporting group description:

Subjects received either IV infusion of Topotecan at a dose of 1.50 mg/m^2 for subjects with calculated creatinine clearance (CrCL) more than or equal to (>=) 60 milliliter per minutes (mL/min); 1.25 mg/m^2 for subjects with CrCL between 40 and 59 mL/min; 0.75 mg/m2 for subjects with CrCL between 30 and 39 mL/min on Days 1 to5 q3wk or IV infusion Cyclophosphamide (CTX) 1000 mg/m^2 in combination with IV infusion of Doxorubicin (DOX) at a dose of 45.0 mg/m^2 and Vincristine (VCR) at a dose of 2.0 (mg) flat dose (FD) on Day 1 q3wk for up to ten cycles. Then, if applicable, DOX was discontinued and the subjects received maintenance treatment until PD, subject's refusal or unacceptable toxicity despite applicable dose reductions.

Reporting group values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan	Total
Number of subjects	307	306	613
Age categorical Units: Subjects			
Age continuous Units: years			
median	63.0	63.0	
full range (min-max)	19 to 83	37 to 82	-
Gender categorical Units: Subjects			
Female	131	133	264
Male	176	173	349

End points

End points reporting groups

Reporting group title	Lurbinectedin + Doxorubicin

Reporting group description:

Subjects received intravenous (IV) infusion of Doxorubicin at a dose of 40.0 milligrams per meter square (mg/m^2) on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m^2 over one hour on Day 1 every three weeks (q3wk) up to ten cycles. Then, if applicable, Doxorubicin was discontinued and the subjects received maintenance treatment along with Lurbinectedin alone intravenously on Day 1 q3wk at a dose of 3.2 mg/m^2 (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m^2 (if more than one dose reduction applied while on combination therapy) until progressive disease (PD), subject refusal or unacceptable toxicity despite applicable dose reductions.

Reporting group title	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Reporting group description:

Subjects received either IV infusion of Topotecan at a dose of 1.50 mg/m^2 for subjects with calculated creatinine clearance (CrCL) more than or equal to (>=) 60 milliliter per minutes (mL/min); 1.25 mg/m^2 for subjects with CrCL between 40 and 59 mL/min; 0.75 mg/m2 for subjects with CrCL between 30 and 39 mL/min on Days 1 to5 q3wk or IV infusion Cyclophosphamide (CTX) 1000 mg/m^2 in combination with IV infusion of Doxorubicin (DOX) at a dose of 45.0 mg/m^2 and Vincristine (VCR) at a dose of 2.0 (mg) flat dose (FD) on Day 1 q3wk for up to ten cycles. Then, if applicable, DOX was discontinued and the subjects received maintenance treatment until PD, subject's refusal or unacceptable toxicity despite applicable dose reductions.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). Intention-to-Treat (ITT) Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated.

End point type	Primary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: months				
median (confidence interval 95%)	8.6 (7.1 to 9.4)	7.6 (6.6 to 8.2)		

Statistical analyses

Statistical analysis title	Lurbinectedin+Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9022
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.967
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.815
upper limit	1.148

Secondary: Difference in Overall Survival Between Lurbinectedin+Doxorubicin and Cyclophosphamide+Doxorubicin+Vincristine in Subjects with CAV as Best Investigator's Choice

End point title	Difference in Overall Survival Between Lurbinectedin+Doxorubicin and Cyclophosphamide+Doxorubicin+Vincristine in Subjects with CAV as Best Investigator's Choice

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	179		
Units: months				
median (confidence interval 95%)				
At 12 months	29.6 (22.8 to 36.3)	24.4 (17.9 to 31.0)		
At 18 months	13.9 (8.8 to 19.1)	15.9 (10.3 to 21.4)		
At 24 months	8.6 (4.1 to 13.1)	8.7 (4.1 to 13.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECISTv1.1) Assessed by Independent Review Committee (IRC)

End point title	Progression-free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECISTv1.1) Assessed by Independent Review Committee (IRC)

End point description:

PFS was defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the subject received further antitumor therapy or was lost to follow-up before pharmacodynamic (PD), PFS was censored at the date of last tumor assessment before the date of subsequent antitumor therapy. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: months				
median (confidence interval 95%)	4.0 (2.8 to 4.2)	4.0 (3.0 to 4.1)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3257
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.831

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.693
upper limit	0.996

Secondary: Number of Subjects With Best Antitumor Response Rate According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) Assessed by Independent Review Committee (IRC)

End point title	Number of Subjects With Best Antitumor Response Rate According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) Assessed by Independent Review Committee (IRC)

End point description:

Best antitumor response was defined as best response obtained in any evaluation according to RECIST v.1.1. Complete Response (CR): disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<) 10 millimetre (mm). Partial Response (PR):at least 30 percentage (%) decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. Progressive Disease (PD):at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. Stable Disease (SD):neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference smallest sum diameters. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Time from date of randomization, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: subjects				
number (not applicable)				
CR	8	4		
PR	89	87		
SD	111	116		
PD	74	52		
Unknown	25	47		
Overall Response Rate (ORR)	97	91		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) Assessed by Independent Review Committee (IRC)

End point title	Duration of Response (DoR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v.1.1) Assessed by Independent Review Committee (IRC)

End point description:

DoR was defined as duration from date of first documentation of response per RECIST v.1.1 (CR or PR, whichever comes first) to the date of documented PD or death. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR:at least 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. If the subjects received further antitumor therapy or is lost to follow-up before PD, DoR was censored at the date of last tumor assessment. ITT population. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	91		
Units: months				
median (confidence interval 95%)	5.7 (4.1 to 7.1)	3.8 (2.8 to 4.3)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	188
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0012
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.416
upper limit	0.81

Secondary: Overall Survival (OS) in Subjects With Chemotherapy-free Interval (CTFI) Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point title	Overall Survival (OS) in Subjects With Chemotherapy-free Interval (CTFI) Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	205		
Units: months				
median (confidence interval 95%)	10.3 (9.0 to 11.8)	8.7 (7.8 to 9.8)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.744
upper limit	1.14

Secondary: Progression-free Survival (PFS) in Subjects With Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point title	Progression-free Survival (PFS) in Subjects With Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point description:

PFS was defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the subject received further antitumor therapy or was lost to follow-up before PD, PFS was censored at the date of last tumor assessment before the date of subsequent antitumor therapy. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	205		
Units: months				
median (confidence interval 95%)	4.8 (4.1 to 5.6)	4.4 (4.0 to 5.3)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	413
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.688
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.549
upper limit	0.863

Secondary: Number of Subjects With Best Antitumor Response Rate in Subjects with Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the

Independent Review Committee

End point title	Number of Subjects With Best Antitumor Response Rate in Subjects with Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point description:

Best antitumor response rate was defined as best response obtained in any evaluation according to RECIST v.1.1. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR: at least 30 % decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference smallest sum diameters. Analysis was performed on the ITT population. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	208	205		
Units: subjects				
number (not applicable)				
CR	8	4		
PR	69	68		
SD	85	73		
PD	32	35		
Unknown	14	25		
ORR	77	72		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) in Subjects with Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point title	Duration of Response (DoR) in Subjects with Chemotherapy-free Interval Greater Than or Equal to (>=) 90 Days Assessed by the Independent Review Committee

End point description:

DoR was defined as duration from date of first documentation of response per RECIST v.1.1 (CR or PR, whichever comes first) to the date of documented PD or death. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR:at least 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest

sum on study. In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. If the subjects received further antitumor therapy or is lost to follow-up before PD, DoR was censored at the date of last tumor assessment. ITT population. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	72		
Units: months				
median (confidence interval 95%)	6.9 (4.1 to 8.3)	4.0 (3.0 to 4.8)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.504
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.346
upper limit	0.736

Secondary: Overall Survival (OS) in Subjects With Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point title	Overall Survival (OS) in Subjects With Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: months				
median (confidence interval 95%)	5.7 (4.1 to 6.7)	5.3 (4.2 to 6.1)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.122
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.5

Secondary: Progression-free Survival (PFS) in Subjects With Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point title	Progression-free Survival (PFS) in Subjects With Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point description:

PFS was defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the subject received further antitumor therapy or was lost to follow-up before PD, PFS was censored at the date of last tumor assessment before the date of subsequent antitumor therapy. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: months				
median (confidence interval 95%)	1.6 (1.4 to 2.7)	2.8 (2.5 to 3.0)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.306
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.955
upper limit	1.786

Secondary: Number of Subjects with Best Antitumor Response Rate in Subjects with Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point title	Number of Subjects with Best Antitumor Response Rate in Subjects with Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point description:

Best antitumor response rate was defined as best response obtained in any evaluation according to RECIST v.1.1. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference smallest sum diameters. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	101		
Units: subjects				
number (not applicable)				
PR	20	19		
SD	26	43		
PD	42	17		
Unknown	11	22		
ORR	20	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) in Subjects with Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point title	Duration of Response (DoR) in Subjects with Chemotherapy-free Interval Less Than [<] 90 Days Assessed by the Independent Review Committee

End point description:

DoR was defined as duration from date of first documentation of response per RECIST v.1.1 (CR or PR, whichever comes first) to the date of documented PD or death. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR:at least 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. If the subjects received further antitumor therapy or is lost to follow-up before PD, DoR was censored at the date of last tumor assessment. ITT population. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: months				

median (confidence interval 95%)	3.0 (1.4 to 4.5)	2.8 (1.4 to 4.1)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.506
upper limit	2.36

Secondary: Overall Survival (OS) in Subjects Without Central Nervous System (CNS) Involvement Assessed by the Independent Review Committee

End point title	Overall Survival (OS) in Subjects Without Central Nervous System (CNS) Involvement Assessed by the Independent Review Committee

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	257		
Units: months				
median (confidence interval 95%)	9.1 (8.1 to 10.2)	7.7 (6.7 to 8.6)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.923
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.765
upper limit	1.113

Secondary: Progression-free Survival (PFS) Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point title	Progression-free Survival (PFS) Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point description:

PFS was defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the subject received further antitumor therapy or was lost to follow-up before PD, PFS was censored at the date of last tumor assessment before the date of subsequent antitumor therapy. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	257		
Units: months				
median (confidence interval 95%)	4.2 (3.7 to 4.8)	4.1 (3.1 to 4.3)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.788
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.645
upper limit	0.961

Secondary: Number of Subjects with Best Antitumor Response Rate Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point title	Number of Subjects with Best Antitumor Response Rate Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point description:

Best antitumor response rate was defined as best response obtained in any evaluation according to RECIST v.1.1. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference smallest sum diameters. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	261	257		
Units: subjects				

number (not applicable)				
CR	7	3		
PR	79	76		
SD	101	100		
PD	55	40		
Unknown	19	38		
ORR	86	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Subjects With Central Nervous System Involvement at Baseline Assessed by the Independent Review Committee

End point title	Overall Survival (OS) in Subjects With Central Nervous System Involvement at Baseline Assessed by the Independent Review Committee

End point description:

OS was defined as the time from the date of randomization to the date of death (death event) or last contact (survival was censored on that date). ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: months				
median (confidence interval 95%)	4.6 (3.1 to 6.1)	6.6 (4.0 to 8.8)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.291
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.838
upper limit	1.99

Secondary: Progression-free Survival (PFS) in Subjects With Central Nervous System Involvement at Baseline Assessed by the Independent Review Committee

End point title	Progression-free Survival (PFS) in Subjects With Central Nervous System Involvement at Baseline Assessed by the Independent Review Committee

End point description:

PFS was defined as the time from the date of randomization to the date of documented progression per RECIST v.1.1 or death (regardless of the cause of death). If the subject received further antitumor therapy or was lost to follow-up before PD, PFS was censored at the date of last tumor assessment before the date of subsequent antitumor therapy. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: months				
median (confidence interval 95%)	1.9 (1.4 to 2.7)	2.8 (1.4 to 3.8)		

Statistical analyses

Statistical analysis title	Lurbinectedin/Doxorubicin, CAV or Topotecan
Comparison groups	Lurbinectedin + Doxorubicin v Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.824
upper limit	2.019

Secondary: Number of Subjects With Adverse Events and Serious Adverse Events (SAE) According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v.4)

End point title	Number of Subjects With Adverse Events and Serious Adverse Events (SAE) According to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v.4)

End point description:

An AE was defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which did not necessarily have a causal relationship with the clinical trial treatment. An SAE was defined as any adverse experience occurring at any dose that resulted in death; was life-threatening; required or prolonged inpatient hospitalization; resulted in persistent or significant disability or incapacity; congenital anomaly or birth defect; medically significant; or any suspected transmission of an infectious agent via a medicinal product. Safety population included subjects who received at least part of one infusion of the investigational agents, and analyzed in the group where they were treated.

End point type	Secondary

End point timeframe:

Time from randomization assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	289		
Units: subjects				
number (not applicable)				
AEs	292	284		
SAEs	126	141		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities Grade Greater than or equal to 3

End point title	Number of Subjects With Laboratory Abnormalities Grade Greater than or equal to 3

End point description:

Number of subjects with laboratory abnormalities >=3 were reported. safety population included subjects who received at least part of one infusion of the investigational agents, and analyzed in the group where they were treated.

End point type	Secondary

End point timeframe:

Time from randomization assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	303	289		
Units: subjects				
number (not applicable)	67	79		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR) Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point title	Duration of Response (DoR) Without Central Nervous System Involvement Assessed by the Independent Review Committee

End point description:

DoR was defined as duration from date of first documentation of response per RECIST v.1.1 (CR or PR, whichever comes first) to the date of documented PD or death. CR: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR:at least 30% decrease in sum of diameters of target lesions, taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. If the subjects received further antitumor therapy or is lost to follow-up before PD, DoR was censored at the date of last tumor assessment. ITT population. Here, "Number of subjects analysed" were those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	79		
Units: months				
median (confidence interval 95%)	5.7 (4.1 to 7.3)	4.0 (3.0 to 4.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Best Antitumor Response Rate With Central Nervous System Involvement Assessed by the Independent Review Committee

End point title	Number of Subjects with Best Antitumor Response Rate With Central Nervous System Involvement Assessed by the Independent Review Committee

End point description:

Best antitumor response rate was defined as best response obtained in any evaluation according to RECIST v.1.1. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must also demonstrate absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression. SD: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference smallest sum diameters. ITT Population included all subjects randomized to either treatment arm independently of whether received study drug or not, and analyzed in the group where they were allocated. Here, "Number of subjects analysed" signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Time from date of randomization until disease progression or death, assessed up to 3.6 years

End point values	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	49		
Units: subjects				
number (not applicable)				
CR	1	1		
PR	10	11		
SD	10	16		
PD	19	12		
Unknown	6	9		
ORR	11	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from randomization up to 3.6 years.

Adverse event reporting additional description:

safety population included subjects who received at least part of one infusion of the investigational agents, and analyzed in the group where they were treated.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Lurbinectedin + Doxorubicin

Reporting group description:

Subjects received IV infusion of Doxorubicin at a dose of 40.0 mg/m^2 on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m^2 over one hour on Day 1 q3wk up to ten cycles. Then, if applicable, Doxorubicin was discontinued and the subjects received maintenance treatment along with Lurbinectedin alone intravenously on Day 1 q3wk at a dose of 3.2 mg/m^2 (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m^2 (if more than one dose reduction applied while on combination therapy) until PD, subject refusal or unacceptable toxicity despite applicable dose reductions.

Reporting group title	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan

Reporting group description:

Subjects received either IV infusion of Topotecan at a dose of 1.50 mg/m^2 for subjects with calculated CrCL >=60 mL/min; 1.25 mg/m^2 for subjects with CrCL between 40 and 59 mL/min; 0.75 mg/m2 for subjects with CrCL between 30 and 39 mL/min on Days 1 to5 q3wk or IV infusion Cyclophosphamide 1000 mg/m^2in combination with IV infusion of DOX at a dose of 45.0 mg/m^2 and Vincristine at a dose of 2.0 mg FD on Day 1 q3wk for up to ten cycles. Then, if applicable, DOX was discontinued and the subjects received maintenance treatment until PD, subject’s refusal or unacceptable toxicity despite applicable dose reductions.

Serious adverse events	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan	
Total subjects affected by serious adverse events			
subjects affected / exposed	126 / 303 (41.58%)	141 / 289 (48.79%)	
number of deaths (all causes)	264	248	
number of deaths resulting from adverse events	19	22	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			

subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery thrombosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	2 / 303 (0.66%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Complication associated with device			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Face oedema			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	4 / 303 (1.32%)	7 / 289 (2.42%)	
occurrences causally related to treatment / all	2 / 4	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 303 (2.31%)	9 / 289 (3.11%)	
occurrences causally related to treatment / all	2 / 8	3 / 11	
deaths causally related to treatment / all	0 / 1	0 / 2	
Infusion site extravasation			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	4 / 303 (1.32%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 303 (0.66%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 303 (0.33%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			

Prostatitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 303 (0.33%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Acute respiratory failure			
subjects affected / exposed	2 / 303 (0.66%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	1 / 1	1 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 303 (0.99%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 303 (3.30%)	4 / 289 (1.38%)	
occurrences causally related to treatment / all	0 / 12	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 0	
Cough			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypoxia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Mediastinal disorder			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 303 (1.32%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 303 (0.66%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 303 (1.65%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infiltration			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Confusional state			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 303 (0.33%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 303 (0.33%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Coronary artery stenosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			

subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post herpetic neuralgia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression			

subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central pain syndrome			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 303 (0.00%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			

subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 303 (3.30%)	22 / 289 (7.61%)	
occurrences causally related to treatment / all	14 / 17	27 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	12 / 303 (3.96%)	24 / 289 (8.30%)	
occurrences causally related to treatment / all	12 / 12	24 / 25	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 303 (0.33%)	4 / 289 (1.38%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 303 (1.32%)	21 / 289 (7.27%)	
occurrences causally related to treatment / all	5 / 5	27 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	9 / 303 (2.97%)	19 / 289 (6.57%)	
occurrences causally related to treatment / all	16 / 16	37 / 37	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			

subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic atrophy			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 303 (0.33%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 303 (0.99%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal motility disorder			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			

subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 303 (0.99%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 303 (0.66%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Oesophagitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 303 (0.33%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	5 / 303 (1.65%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 303 (0.66%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 303 (0.33%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	5 / 303 (1.65%)	11 / 289 (3.81%)	
occurrences causally related to treatment / all	0 / 5	5 / 12	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonia			
subjects affected / exposed	14 / 303 (4.62%)	12 / 289 (4.15%)	
occurrences causally related to treatment / all	2 / 18	3 / 12	
deaths causally related to treatment / all	1 / 6	0 / 0	
Sepsis			
subjects affected / exposed	3 / 303 (0.99%)	6 / 289 (2.08%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	1 / 2	
Subcutaneous abscess			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 303 (0.33%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 303 (0.00%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 303 (0.00%)	8 / 289 (2.77%)	
occurrences causally related to treatment / all	0 / 0	6 / 8	
deaths causally related to treatment / all	0 / 0	5 / 6	
Upper respiratory tract infection			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 303 (0.33%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	4 / 303 (1.32%)	3 / 289 (1.04%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 303 (0.66%)	0 / 289 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	7 / 303 (2.31%)	6 / 289 (2.08%)	
occurrences causally related to treatment / all	0 / 11	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 303 (0.00%)	2 / 289 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 303 (0.00%)	1 / 289 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Lurbinectedin + Doxorubicin	Cyclophosphamide + Doxorubicin+ Vincristine (CAV) or Topotecan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	292 / 303 (96.37%)	284 / 289 (98.27%)	
Investigations			
Ejection fraction decreased			
subjects affected / exposed	16 / 303 (5.28%)	9 / 289 (3.11%)	
occurrences (all)	17	11	

Weight decreased			
subjects affected / exposed	64 / 303 (21.12%)	38 / 289 (13.15%)	
occurrences (all)	79	44	
Vascular disorders			
Hypotension			
subjects affected / exposed	19 / 303 (6.27%)	17 / 289 (5.88%)	
occurrences (all)	25	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	28 / 303 (9.24%)	23 / 289 (7.96%)	
occurrences (all)	31	26	
Headache			
subjects affected / exposed	30 / 303 (9.90%)	32 / 289 (11.07%)	
occurrences (all)	33	33	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	121 / 303 (39.93%)	173 / 289 (59.86%)	
occurrences (all)	341	533	
Leukopenia			
subjects affected / exposed	28 / 303 (9.24%)	78 / 289 (26.99%)	
occurrences (all)	106	200	
Lymphopenia			
subjects affected / exposed	15 / 303 (4.95%)	23 / 289 (7.96%)	
occurrences (all)	51	82	
Neutropenia			
subjects affected / exposed	101 / 303 (33.33%)	181 / 289 (62.63%)	
occurrences (all)	316	424	
Thrombocytopenia			
subjects affected / exposed	70 / 303 (23.10%)	132 / 289 (45.67%)	
occurrences (all)	246	406	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	164 / 303 (54.13%)	143 / 289 (49.48%)	
occurrences (all)	365	314	
Mucosal inflammation			

subjects affected / exposed	30 / 303 (9.90%)	19 / 289 (6.57%)	
occurrences (all)	50	31	
Non-cardiac chest pain			
subjects affected / exposed	26 / 303 (8.58%)	20 / 289 (6.92%)	
occurrences (all)	27	25	
Oedema			
subjects affected / exposed	21 / 303 (6.93%)	20 / 289 (6.92%)	
occurrences (all)	24	21	
Pyrexia			
subjects affected / exposed	28 / 303 (9.24%)	33 / 289 (11.42%)	
occurrences (all)	32	47	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 303 (4.62%)	24 / 289 (8.30%)	
occurrences (all)	17	29	
Constipation			
subjects affected / exposed	59 / 303 (19.47%)	55 / 289 (19.03%)	
occurrences (all)	90	76	
Diarrhoea			
subjects affected / exposed	43 / 303 (14.19%)	48 / 289 (16.61%)	
occurrences (all)	65	59	
Nausea			
subjects affected / exposed	123 / 303 (40.59%)	88 / 289 (30.45%)	
occurrences (all)	219	118	
Vomiting			
subjects affected / exposed	72 / 303 (23.76%)	48 / 289 (16.61%)	
occurrences (all)	125	53	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	60 / 303 (19.80%)	49 / 289 (16.96%)	
occurrences (all)	80	59	
Dyspnoea			
subjects affected / exposed	52 / 303 (17.16%)	48 / 289 (16.61%)	
occurrences (all)	63	56	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	34 / 303 (11.22%)	36 / 289 (12.46%)	
occurrences (all)	40	45	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 303 (4.29%)	15 / 289 (5.19%)	
occurrences (all)	13	19	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 303 (7.92%)	15 / 289 (5.19%)	
occurrences (all)	29	17	
Back pain			
subjects affected / exposed	37 / 303 (12.21%)	33 / 289 (11.42%)	
occurrences (all)	49	43	
Infections and infestations			
Pharyngitis			
subjects affected / exposed	19 / 303 (6.27%)	12 / 289 (4.15%)	
occurrences (all)	26	13	
Lower respiratory tract infection			
subjects affected / exposed	18 / 303 (5.94%)	21 / 289 (7.27%)	
occurrences (all)	24	29	
Pneumonia			
subjects affected / exposed	10 / 303 (3.30%)	15 / 289 (5.19%)	
occurrences (all)	12	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	85 / 303 (28.05%)	60 / 289 (20.76%)	
occurrences (all)	129	88	
Hypokalaemia			
subjects affected / exposed	25 / 303 (8.25%)	25 / 289 (8.65%)	
occurrences (all)	41	38	
Hyponatraemia			
subjects affected / exposed	18 / 303 (5.94%)	21 / 289 (7.27%)	
occurrences (all)	25	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 March 2016	Following Changes were made: change in study design; subjects in the control arm were received either topotecan or CAV, according to the Investigator's preference, until the first of these options reaches 55% of the target subjects enrollment (i.e., n=165). Once this has occurred, the subjects remaining to reach 300 randomized subjects in the control arm were received the other option. Information on background, criteria for treatment continuation, dose levels and dose reduction, and study assessment in subjects assigned to CAV in the control arm has been added accordingly. In addition, primary and secondary analyses, statistical methodology and stratification factors were updated; The hemoglobin level required for treatment continuation in both arms were increased from >=8.5 grams per decilitre (g/dl) to >=9.0 g/dl, to be consistent with the approved topotecan Summary of Product Characteristics; Clarifications for consistency were added to the laboratory tests, clinical and radiological tumor assessment and subjects-reported outcomes to be done at the end of treatment; the information on drug-drug interactions has been updated and clarified; as a result of the merger between Zeltia, S.A. and Pharma Mar, S.A., Sociedad Unipersonal, the Sponsor shall now be referred to as Pharma Mar, S.A, without further reference to "Sociedad Unipersonal"; study contact information has been updated; some minor typographic and style edit changes have been added.
03 October 2016	Following changes were made: inclusion criterion #3 has been modified to allow the inclusion of subjects with a CTFI >= 30 days, thereby excluding those with a CTFI <30 days.
03 May 2018	The overall study design has been modified to change the primary endpoint from PFS assessed by an IRC to OS; the overall study design has also been modified to remove the need for restricting subjects assignment in the control arm; To enhance the interpretability of the analyses of secondary endpoints, some of these endpoints have been moved to a list of tertiary endpoints, leaving as secondary those considered more relevant from a clinical point of view (i.e., difference in OS between PM01183/DOX and CAV, in subjects with CAV as best Investigator's choice; OS/PFS per RECIST v.1.1 in subjects with and without baseline CNS involvement; PFS per RECIST v.1.1 by an IRC; antitumor activity as per RECIST v.1.1 by an IRC; and safety profile). The procedure for alpha spending correction is detailed, describing the statistical methods and the formal interim analyses requested by the IDMC; a new secondary objective has been added: to compare differences in OS and PFS in subjects with and without baseline CNS involvement.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported