



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 (\geq) 60 milliliter per minutes (mL/min); 1.25 mg/m^2 for subjects with CrCL between 40 and 59 mL/min ; 0.75 mg/m^2 for subjects with CrCL between 30 and 39 mL/min on Days 1 to 5 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/m²) on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m² 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/m² (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m² (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/m² for subjects with calculated creatinine clearance (CrCL) more than or equal to (\geq) 60 milliliter per minutes (mL/min); 1.25 mg/m² 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 to 5 q3wk or IV infusion Cyclophosphamide (CTX) 1000 mg/m² in combination with IV infusion of Doxorubicin (DOX) at a dose of 45.0 mg/m² 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 full range (min-max) | 63.0 19 to 83 | 63.0 37 to 82 | - |
| Gender categorical Units: Subjects Female Male | 131 176 | 133 173 | 264 349 |

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 (\geq) 60 milliliter per minutes (mL/min); 1.25 mg/m ² for subjects with CrCL between 40 and 59 mL/min; 0.75 mg/m ² for subjects with CrCL between 30 and 39 mL/min on Days 1 to 5 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)

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|---|-----------------------|
| 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

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|-----------------|--|
| 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.

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|----------------|-----------|
| 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 |

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|---------------------|---------|
| 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)

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|-----------------|--|
| 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.

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|----------------|-----------|
| 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.

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|----------------|-----------|
| 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 (\geq) 90 Days Assessed by the Independent Review Committee

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|-----------------|---|
| End point title | Overall Survival (OS) in Subjects With Chemotherapy-free Interval (CTFI) Greater Than or Equal to (\geq) 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 (\geq) 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 (\geq) 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 (\geq) 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 (\geq) 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 (\geq) 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 (\geq) 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/m² on Day 1, followed by IV infusion of Lurbinectedin at a dose of 2.0 mg/m² 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/m² (if no more than one dose reduction applied while on combination therapy), or 2.6 mg/m² (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/m² for subjects with calculated CrCL ≥60 mL/min; 1.25 mg/m² 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 to 5 q3wk or IV infusion Cyclophosphamide 1000 mg/m² in combination with IV infusion of DOX at a dose of 45.0 mg/m² 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 | |

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|---|-----------------|-----------------|--|
| 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 | | | |

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|---|------------------|-----------------|--|
| 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 | |

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|---|-----------------|-----------------|--|
| 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 | | | |

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

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

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