# Clinical trial results:
# An Open-Label, Randomized, Parallel Group Study of Patients Treated with Paclitaxel with Standard Dosing versus Pharmacokinetic Guided Dose Adjustment in Patients with Advanced NSCLC

## Summary

| | |
|---|---|
| EudraCT number | 2010-023688-16 |
| Trial protocol | DE |
| Global end of trial date | 25 December 2014 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 05 September 2018 |
| First version publication date | 05 September 2018 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | C-III-002 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01326767 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Central European Society for Anticancer Drug Research |
| Sponsor organisation address | Hanglüssgasse, 4/1-3, Wien, Austria, 1150 |
| Public contact | Clinical trials information, Central European Society for Anticancer Drug Research, max.roessler@cesar.or.at |
| Scientific contact | Clinical trials information, Central European Society for Anticancer Drug Research, max.roessler@cesar.or.at |

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 | 20 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 December 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 December 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the CEPAC-TDM study is to apply individualized paclitaxel dosing in patients with advanced NSCLC, as defined in Section 1.4. By applying the prespecified dosing algorithm, grade 4 neutropenia is predicted to be reduced from 15% with conventional dosing (i.e. paclitaxel 200 mg/m2 in combination with carboplatin or cisplatin at the predefined dose, given every three weeks) (Arm A) to 4% with individualized paclitaxel dosing (in combination with carboplatin or cisplatin at the predefined dose, given every three weeks) (Arm B) during the second treatment cycle. At the same time, progression-free survival (PFS) and overall survival (OS) must not be affected by individualized paclitaxel dosing.

Protection of trial subjects:

As far as possible, patients were treated according to clinical routine. Study specific intervention was kept to a minimum. Patient specific dose modifications were designed to reduce adverse events.

Background therapy:

Cisplatin / Carboplatin

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 25 March 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 317 |
| Country: Number of subjects enrolled | Switzerland: 49 |
| Worldwide total number of subjects | 366 |
| EEA total number of subjects | 317 |

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) | 199 |
| From 65 to 84 years | 167 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

One study site in Switzerland participated in the study and 10 German study sites. Recruitment started on 25.03.2011 and ended at 25.04.2014 as the last patient was recruited.

### Pre-assignment

Screening details:

The screening criteria were defined by the inclusion and exclusion criteria as defined in the study protocol.

### Period 1

| | |
|---|---|
| Period 1 title | Treatment period |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

No blinding used

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Standard treatment arm (A) |

Arm description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg/m2 every 3 weeks for a maximum of 6 cycles

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

80 mg/m2 on day 1 or
40 mg/m2 days 1 & 2

every 3 weeks for a maximum of 6 cycles

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

AUC6 every three weeks for a maximum of 6 cycles

| **Arm title** | Experimental treatment arm |
|---|---|

Arm description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Individual dose adaptation based on PK values

| Investigational medicinal product name | Cisplatin |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

80 mg/m2 on day 1 or
40 mg/m2 days 1 & 2

every 3 weeks for a maximum of 6 cycles

| Investigational medicinal product name | Carboplatin |
|---|---|
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

AUC6 every three weeks for a maximum of 6 cycles

| **Number of subjects in period 1** | Standard treatment arm (A) | Experimental treatment arm |
|---|---|---|
| Started | 183 | 183 |
| Completed | 183 | 183 |

## Period 2

| | |
|---|---|
| Period 2 title | Follow up period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Standard treatment arm (A) |

Arm description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

200 mg/m2 every 3 weeks for a maximum of 6 cycles

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

80 mg/m2 on day 1 or
40 mg/m2 days 1 & 2

every 3 weeks for a maximum of 6 cycles

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

AUC6 every three weeks for a maximum of 6 cycles

| | |
|---|---|
| **Arm title** | Experimental treatment arm |

Arm description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral

neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Individual dose adaptation based on PK values

| | |
|---|---|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

80 mg/m2 on day 1 or
40 mg/m2 days 1 & 2

every 3 weeks for a maximum of 6 cycles

| | |
|---|---|
| Investigational medicinal product name | Carboplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

AUC6 every three weeks for a maximum of 6 cycles

| **Number of subjects in period 2** | Standard treatment arm (A) | Experimental treatment arm |
|---|---|---|
| Started | 183 | 183 |
| Completed | 183 | 183 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Standard treatment arm (A) |

Reporting group description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| Reporting group title | Experimental treatment arm |
|---|---|

Reporting group description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| Reporting group values | Standard treatment arm (A) | Experimental treatment arm | Total |
|---|---|---|---|
| Number of subjects | 183 | 183 | 366 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| ITT Population | | | |
| Units: years | | | |
| arithmetic mean | 63.9 | 62.7 | |
| standard deviation | ± 8.07 | ± 7.59 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 55 | 65 | 120 |
| Male | 128 | 118 | 246 |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population is the primary analysis population for both safety and efficacy analyses, and is defined as patients who are randomized and receive at least one paclitaxel treatment.

| | |
|---|---|
| Subject analysis set title | PP |
| Subject analysis set type | Per protocol |

Subject analysis set description:

The PP population is defined as all patients in the ITT analysis population with no major protocol violations.

| Reporting group values | ITT | PP | |
|---|---|---|---|
| Number of subjects | 366 | 277 | |
| Age categorical<br>Units: Subjects | | | |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over | | | |
| Age continuous | | | |
| ITT Population | | | |
| Units: years<br>arithmetic mean<br>standard deviation | <br>63.3<br>± 7.84 | <br>63.2<br>± 7.85 | |
| Gender categorical<br>Units: Subjects | | | |
| Female<br>Male | 120<br>246 | 89<br>188 | |

## End points

### End points reporting groups

| Reporting group title | Standard treatment arm (A) |
|---|---|

Reporting group description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| Reporting group title | Experimental treatment arm |
|---|---|

Reporting group description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| Reporting group title | Standard treatment arm (A) |
|---|---|

Reporting group description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| Reporting group title | Experimental treatment arm |
|---|---|

Reporting group description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| Subject analysis set title | ITT |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The ITT population is the primary analysis population for both safety and efficacy analyses, and is defined as patients who are randomized and receive at least one paclitaxel treatment.

| Subject analysis set title | PP |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

The PP population is defined as all patients in the ITT analysis population with no major protocol violations.

## Primary: Grade 4 neutropenia at Day 15, Cycle 2

| End point title | Grade 4 neutropenia at Day 15, Cycle 2 |
|---|---|

End point description:

The primary objective of the CEPAC-TDM study is to apply individualized paclitaxel dosing in patients with advanced NSCLC, as defined in Section 1.4. By applying the prespecified dosing algorithm, grade 4 neutropenia is predicted to be reduced from 15% with conventional dosing (i.e. paclitaxel 200 mg/m2 in combination with carboplatin at the predefined dose, given every three weeks) (Arm A) to 4% with individualized paclitaxel dosing (in combination with carboplatin at the predefined dose, given every three weeks) (Arm B) during the second treatment cycle. At the same time, progression-free survival (PFS) and overall survival (OS) must not be affected by individualized paclitaxel dosing.

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

End point timeframe:

Grade 4 neutropenia Day 15, Cycle 2 (as identified from hematology safety laboratory)

| **End point values** | Standard treatment arm (A) | Experimental treatment arm | ITT | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 138 | 145 | 366 | |
| Units: Grade 4 neutropenia Cycle 2 Yes/No | 23 | 23 | 46 | |

| **Attachments (see zip file)** | Primary Endpoint/Table primary Endpoint.PNG |
|---|---|

### Statistical analyses

| **Statistical analysis title** | Fisher exact test on primary endpoint |
|---|---|

Statistical analysis description:

Fisher exact test on percentage of subjects with Grade 4 neutropenia at Day 15, Cycle 2 (based on number of subjects with available information)

| Comparison groups | Experimental treatment arm v Standard treatment arm (A) |
|---|---|
| Number of subjects included in analysis | 283 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8733 |
| Method | Fisher exact |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

| **Statistical analysis title** | Logistic regression on primary endpoint |
|---|---|

Statistical analysis description:

Baseline variables age (<65 vs. >=65), gender, tumor stage (IIIB, IV), smoking status (never smoked vs. former smoker vs. current smoker), tumor histology (non-squamous adenocarcinoma vs. squamous cell carcinoma), baseline ECOG performance status (0 vs. 1 vs. 2), prior treatment (yes/no), platinum drug (cisplatin, carboplatin), the presence of brain metastases at baseline assessment, and treatment group allocation (i.e. study arm) were taken as covariates

| | |
|---|---|
| Comparison groups | Standard treatment arm (A) v Experimental treatment arm |
| Number of subjects included in analysis | 283 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5847 |
| Method | Regression, Logistic |

## Secondary: Progression-free survival

| | |
|---|---|
| End point title | Progression-free survival |

End point description:

A Cox regression model was applied for PFS that included the following covariates: treatment arm, age group (older than 65 or 65 vs. younger than 65), gender, tumor stage (IIIB vs. IV), smoking status, tumor histology (non-squamous adenocarcinoma vs. squamous cell carcinoma), Baseline ECOG (0 vs. 1 vs. 2), pre-treatment performed, platinum compound. Note that only the patients to be compared with respect to these parameters were included, e.g. only patients with non-squamous adenocarcinoma or squamous cell carcinoma.

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

End point timeframe:

Progression-free survival is the time from first administration of study medication to progression or death. Patients without progression or death were censored at their last available response assessment.

| **End point values** | Standard treatment arm (A) | Experimental treatment arm | ITT | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 183 | 183 | 0[1] | |
| Units: Days | | | | |
| median (standard error) | 169 (± 0.039) | 153 (± 0.038) | () | |

Notes:

[1] - No pooled analysis performed for whole ITT population

### Statistical analyses

| **Statistical analysis title** | Progression-free survival: Log-rank test |
|---|---|

Statistical analysis description:

Log-rank test for PFS to compare the two study arms in the ITT population

| | |
|---|---|
| Comparison groups | Standard treatment arm (A) v Experimental treatment arm |
| Number of subjects included in analysis | 366 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1786 |
| Method | Logrank |

| **Statistical analysis title** | Progression-free survival: Cox regression |
|---|---|
| Comparison groups | Experimental treatment arm v Standard treatment arm (A) |

| | |
|---|---|
| Number of subjects included in analysis | 366 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2896 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.1468 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.89 |
| upper limit | 1.4779 |

## Secondary: Overall survival

| | |
|---|---|
| End point title | Overall survival |

End point description:

A Cox regression model was applied for OS that included the following covariates: treatment arm, age group (older than 65 or 65 vs. younger than 65), gender, tumor stage (IIIB vs. IV), smoking status, tumor histology (non-squamous adenocarcinoma vs. squamous cell carcinoma), Baseline ECOG (0 vs. 1 vs. 2), pre-treatment performed, platinum compound. Note that only the patients to be compared with respect to these parameters were included, e.g. only patients with non-squamous adenocarcinoma or squamous cell carcinoma.

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

End point timeframe:

Overall survival (OS) is time from first administration of study medication to date of death. Patients that did not die were censored at last date patient was seen alive.

| **End point values** | Standard treatment arm (A) | Experimental treatment arm | ITT | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 182 | 183 | 0[2] | |
| Units: Days | | | | |
| median (standard error) | 359 (± 0.04) | 287 (± 0.039) | () | |

Notes:

[2] - No pooled analysis of overall survival performed for whole ITT population

## Statistical analyses

| **Statistical analysis title** | Overall survival: Log-rank test |
|---|---|
| Comparison groups | Standard treatment arm (A) v Experimental treatment arm |
| Number of subjects included in analysis | 365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0398 |
| Method | Logrank |

| **Statistical analysis title** | Overall survival: Cox regression |
|---|---|
| Comparison groups | Standard treatment arm (A) v Experimental treatment arm |
| Number of subjects included in analysis | 365 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0404 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.0136 |
| upper limit | 1.8247 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs have been assessed from first study drug administration to the End of treatment visit.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Standard treatment arm (A) |

Reporting group description:

Chemotherapy will be administered according to the SmPC for Paclitaxel and Carboplatin (see Appendix 2-4), with initial doses according to Table 6.1.1. Dosing adaptation is performed according to specifications as outlined in Section 6.2. Rounding of chemotherapy dosage is left to the treating physician. The Body surface area (BSA) is calculated by the Dubois formula for Paclitaxel. A maximum BSA of 2.0 m2 may be used for dosing calculation according to local practice.

| | |
|---|---|
| Reporting group title | Experimental treatment arm (B) |

Reporting group description:

First-cycle Paclitaxel dose is adapted according to patient gender and age. Paclitaxel plasma levels will be determined 24 hours after the infusion, and paclitaxel TC>0.05 is calculated by using NONMEM. Individual paclitaxel dose adjustments for cycles two to six are done according to previous-cycle individual paclitaxel TC>0.05 and categorical neutropenia according to the algorithm. For each dose adaptation, only Paclitaxel TC>0.05 and neutrophil nadir from the prior cycle will be used for calculation. Missing values for Paclitaxel TC>0.05 or neutrophil nadir will be replaced by a value of 28 hours (Paclitaxel TC>0.05) and 1.5 G/L (neutrophil nadir), respectively. In case both Paclitaxel TC>0.05 and neutrophil nadir are missing, dose adaptations will be performed as recommended for the conventional treatment arm (Arm A). As a safety measure to prevent cumulative peripheral neuropathy, Paclitaxel dose increase is limited to a maximum of 320 mg/m2 in the experimental treatm. arm

| Serious adverse events | Standard treatment arm (A) | Experimental treatment arm (B) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 114 / 183 (62.30%) | 127 / 183 (69.40%) | |
| number of deaths (all causes) | 111 | 131 | |
| number of deaths resulting from adverse events | 7 | 11 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Neoplasm progression | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Neoplasm malignant | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Embolism | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral artery occlusive disease | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 183 (3.28%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (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 | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 183 (2.19%) | 8 / 183 (4.37%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|---|---|---|
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Disorientation | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental disorder due to a general medical condition | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Rib fracture | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Polyneuropathy | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 183 (0.00%) | 3 / 183 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery occlusion | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 183 (3.83%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 9 / 9 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 183 (1.64%) | 5 / 183 (2.73%) | |
| occurrences causally related to treatment / all | 5 / 5 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 4 / 4 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 5 / 183 (2.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 3 / 183 (1.64%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 3 / 3 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 7 / 183 (3.83%) | |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 183 (1.64%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal perforation | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer perforation | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal ischaemia | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal stenosis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatorenal syndrome | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| sepsis | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Infection | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 3 / 183 (1.64%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 11 / 183 (6.01%) | 4 / 183 (2.19%) | |
| occurrences causally related to treatment / all | 2 / 13 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 2 / 183 (1.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung abscess | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mediastinal abscess | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral infection | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 183 (0.55%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 183 (1.64%) | 0 / 183 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 183 (0.55%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 183 (0.00%) | 1 / 183 (0.55%) | |
| 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** | Standard treatment arm (A) | Experimental treatment arm (B) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 144 / 183 (78.69%) | 145 / 183 (79.23%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 10 / 183 (5.46%) | 11 / 183 (6.01%) | |
| occurrences (all) | 17 | 25 | |
| Nervous system disorders | | | |
| Polyneuropathy | | | |
| subjects affected / exposed | 58 / 183 (31.69%) | 37 / 183 (20.22%) | |
| occurrences (all) | 74 | 40 | |
| Peripheral sensory neuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 183 (6.01%) | 5 / 183 (2.73%) | |
| occurrences (all) | 11 | 5 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 19 / 183 (10.38%) | 43 / 183 (23.50%) | |
| occurrences (all) | 32 | 79 | |
| Anaemia | | | |
| subjects affected / exposed | 24 / 183 (13.11%) | 20 / 183 (10.93%) | |
| occurrences (all) | 32 | 30 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 183 (1.09%) | 11 / 183 (6.01%) | |
| occurrences (all) | 2 | 21 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 58 / 183 (31.69%) | 42 / 183 (22.95%) | |
| occurrences (all) | 71 | 45 | |
| pain | | | |
| subjects affected / exposed | 13 / 183 (7.10%) | 12 / 183 (6.56%) | |
| occurrences (all) | 19 | 13 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 28 / 183 (15.30%) | 25 / 183 (13.66%) | |
| occurrences (all) | 40 | 30 | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 183 (8.74%) | 18 / 183 (9.84%) | |
| occurrences (all) | 18 | 19 | |
| Constipation | | | |
| subjects affected / exposed | 14 / 183 (7.65%) | 14 / 183 (7.65%) | |
| occurrences (all) | 14 | 15 | |
| Vomiting | | | |
| subjects affected / exposed | 9 / 183 (4.92%) | 11 / 183 (6.01%) | |
| occurrences (all) | 12 | 18 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 13 / 183 (7.10%) | 15 / 183 (8.20%) | |
| occurrences (all) | 14 | 16 | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | 14 / 183 (7.65%) | |
| occurrences (all) | 12 | 14 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 27 / 183 (14.75%) | 34 / 183 (18.58%) | |
| occurrences (all) | 27 | 34 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 28 / 183 (15.30%) | 20 / 183 (10.93%) | |
| occurrences (all) | 44 | 32 | |
| Arthralgia | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | 7 / 183 (3.83%) | |
| occurrences (all) | 15 | 7 | |
| Myalgia | | | |
| subjects affected / exposed | 12 / 183 (6.56%) | 8 / 183 (4.37%) | |
| occurrences (all) | 16 | 13 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 17 / 183 (9.29%) | 11 / 183 (6.01%) | |
| occurrences (all) | 17 | 14 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 14 June 2011 | This amendment was prepared to implement a biomarker sub study to increase the scientific value of this study. This sub-study has been set up and is supervised by Dr. Holdenrieder (Institute for clinical Chemistry and clinical Pharmacology University Clinic Bonn, Sigmund-Freud-Str. 25 53105 Bonn, Germany). The aim of the study is to test biomarkers for their predictive and prognostic value as well as to determine if the kinetics of biomarker plasma levels allows monitoring of treatment success and toxicities. To minimized extra efforts for the patients, the time points for the blood analysis have been chosen in a way that no extra venipunctures are required. The blood draws for this sub-study will be done together with the ones for the main study. |
| 25 July 2013 | This amendment was prepared since the ongoing safety monitoring of the study showed, that the pharmacokinetic dose adaptation of paclitaxel (PTX), compared to the standard dosing in the conventional treatment arm A, in study patients receiving cisplatin leads to an increase of severe neutropenia. Although this did not result in an increase of infect-complications, the steering committee decided not to include any further patients, considered for cisplatin treatment. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

http://www.ncbi.nlm.nih.gov/pubmed/27502710