



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
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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	Hanglössgasse, 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
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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:

AUC₀₋₆ every three weeks for a maximum of 6 cycles

Arm title	Experimental treatment arm
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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			
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			
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			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
ITT Population			
Units: years			
arithmetic mean	63.3	63.2	
standard deviation	± 7.84	± 7.85	
Gender categorical			
Units: Subjects			
Female	120	89	
Male	246	188	

End points

End points reporting groups

Reporting group title	Standard treatment arm (A)
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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
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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)
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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
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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
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Subject analysis set type	Intention-to-treat
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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
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Subject analysis set type	Per protocol
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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
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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
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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
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Statistical analyses

Statistical analysis title	Fisher exact test on primary endpoint
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	15.1
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Reporting groups

Reporting group title	Standard treatment arm (A)
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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)
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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			

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			

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			

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 occurrences (all)	11 / 183 (6.01%) 11	5 / 183 (2.73%) 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 occurrences (all)	12 / 183 (6.56%) 12	14 / 183 (7.65%) 14	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	27 / 183 (14.75%) 27	34 / 183 (18.58%) 34	
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	28 / 183 (15.30%) 44 12 / 183 (6.56%) 15 12 / 183 (6.56%) 16	20 / 183 (10.93%) 32 7 / 183 (3.83%) 7 8 / 183 (4.37%) 13	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	17 / 183 (9.29%) 17	11 / 183 (6.01%) 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>