Clinical trial results:
Prospective Randomized Phase-III-Trial of Paclitaxel plus Topotecan versus Topotecan plus Cisplatin in Recurrent or Persistent Cervical Carcinoma

Summary

EudraCT number	2006-000349-20
Trial protocol	DE AT BE
Global end of trial date	02 April 2014

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	IFG-01-0106

Additional study identifiers

ISRCTN number	ISRCTN77165120
ClinicalTrials.gov id (NCT number)	NCT01405235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut für Frauengesundheit GmbH
Sponsor organisation address	Universitätsstraße 21-23, Erlangen, Germany, 91054
Public contact	Clinical Trial Information, Institut für Frauengesundheit GmbH, studien@ifg-erlangen.de
Scientific contact	Clinical Trial Information, Institut für Frauengesundheit GmbH, studien@ifg-erlangen.de

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	23 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 April 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Comparison of overall survival

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the applicable guidelines of the International Conference on Harmonization Good Clinical Practice (GCP) concerning informed consent and the protection of rights of human patients and other relevant international guidelines.

Background therapy: -

Evidence for comparator:

The studies GOG 169 and 179 demonstrated that a combination of paclitaxel and cisplatin was superior to a cisplatin monotherapy
with respect to therapeutic response and progression-free survival, as was a combination of topotecan and cisplatin with respect to therapeutic response, progression-free survival, and total survival. To achieve further improvement in total survival and to answer questions regarding the value of using a platinum-free combination, we conducted this trial to compare the efficacy of a platinum-free combination of paclitaxel and topotecan to a combination of cisplatin and topotecan.

Actual start date of recruitment	22 January 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	15 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 34
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Germany: 127
Worldwide total number of subjects	173
EEA total number of subjects	173

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)	155
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The clinical trial was conducted in 52 trials sites of the organ-specific uterine malignoma group and the organ-specific ovarian
group of the AGO and other clinics with sufficient experience in conducting clinical studies. Recruitment started from January 2007 and was suspended on 31.12.2012.

Pre-assignment

Screening details:

A total of 189 patients were assessed fpr eligibility. 11 Patients declined study participation and 5 subjects were identified as screening failures. Therefore, 173 patients were assessed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel/Topotecan

Arm description:

Paclitaxel 70 mg/m2/d i.v. was administered over one hour and topotecan 1.75 mg/m2/d i.v. over 30 min. on days 1, 8, and 15; this cycle was repeated every four weeks for six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

Arm type	Experimental
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Solution for infusion , Intravenous use

Dosage and administration details:

Paclitaxel 70 mg/m2/d i.v. was administered over one hour on days 1, 8, and 15; this cycle was repeated every four weeks for six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.

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

Dosage and administration details:

Topotecan administered 1.75 mg/m2/d i.v. over 30 min. on Days 1, 8, and 15; this cycle will be repeated every 4 weeks for 6 cycles or until there is evidence of disease progression, or until unacceptable adverse effects prohibit further therapy. Maximum body surface area used for dose calculations will be 2.0 m2.

Arm title	Cisplatin/Topotecan

Arm description:

Topotecan 0.75 mg/m2/d was administered over 30 min. on days 1, 2, and 3 and cisplatin 50 mg/m2 i.v. on day 1; this cycle repeated every three weeks for a maximum of six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

Arm type	Active comparator
Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	Hycamtin
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use, Solution for infusion

Dosage and administration details:

Topotecan administered 1.75 mg/m2/d i.v. over 30 min. on Days 1, 8, and 15; this cycle will be repeated every 4 weeks for 6 cycles or until there is evidence of disease progression, or until unacceptable adverse effects prohibit further therapy. Maximum body surface area used for dose calculations will be 2.0 m2.

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

Dosage and administration details:

Cisplatin 50 mg/m2 i.v. was administered on day 1; this cycle repeated every three weeks for a maximum of six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.

Number of subjects in period 1	Paclitaxel/Topotecan	Cisplatin/Topotecan
Started	88	85
Completed	83	78
Not completed	5	7
Did not receive assigned treatment	5	7

Baseline characteristics

Reporting groups

Reporting group title	Paclitaxel/Topotecan

Reporting group description:

Paclitaxel 70 mg/m2/d i.v. was administered over one hour and topotecan 1.75 mg/m2/d i.v. over 30 min. on days 1, 8, and 15; this cycle was repeated every four weeks for six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

Reporting group title	Cisplatin/Topotecan

Reporting group description:

Topotecan 0.75 mg/m2/d was administered over 30 min. on days 1, 2, and 3 and cisplatin 50 mg/m2 i.v. on day 1; this cycle repeated every three weeks for a maximum of six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

Reporting group values	Paclitaxel/Topotecan	Cisplatin/Topotecan	Total
Number of subjects	88	85	173
Age categorical Units: Subjects			
Adults (18-64 years)			0
From 65-84 years			0
Age continuous Units: years			
arithmetic mean	50.4	49.0	
standard deviation	± 11.1	± 11.0	-
Gender categorical Units: Subjects			
Female	88	85	173
Male	0	0	0
ECOG Units: Subjects			
ECOG 0	44	38	82
ECOG 1	37	39	76
ECOG 2	7	8	15
concomitant diseases			
Number of concomitant diseases			
Units: Subjects			
N=0	32	33	65
N=1	25	24	49
N=2+	31	28	59
Disease status			

Units: Subjects			
Disatant metastasis	66	62	128
Local recurrence	22	23	45
BMI			
Units: kg/m2			
arithmetic mean	26.2	25.6	
standard deviation	± 6.5	± 6.6	-

End points

End points reporting groups

Reporting group title	Paclitaxel/Topotecan

Reporting group description:

Paclitaxel 70 mg/m2/d i.v. was administered over one hour and topotecan 1.75 mg/m2/d i.v. over 30 min. on days 1, 8, and 15; this cycle was repeated every four weeks for six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

Reporting group title	Cisplatin/Topotecan

Reporting group description:

Topotecan 0.75 mg/m2/d was administered over 30 min. on days 1, 2, and 3 and cisplatin 50 mg/m2 i.v. on day 1; this cycle repeated every three weeks for a maximum of six cycles or until there was evidence of disease progression, or until unacceptable adverse effects prohibited further therapy. Maximum body surface area used for dose calculations was 2.0 m2.
Treatment continued until completion of a maximum of six cycles. The therapy discontinued prior to the completion of six cycles if there was evidence of disease progression, or if unacceptable adverse effects prohibited further therapy. Patients with continued response or stable disease could continue to participate in the study for an additional three cycles beyond the original six cycles with consent of the Study Director.

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

Subject analysis set description:

ITT population 1 are all patients included in the interim analysis (n=172) and ITT population 2 (ITT2; n=173) is the total study population

Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety evaluation was performed in all randomized patients who were treated with at least one cycle of chemotherapy (n=161 (Safety Population); Arm A (Paclitaxel and Topotecan) 83 patients and Arm B (control group; Topotecan and Cisplatin) 78 patients).

Primary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival is the observed length of life from randomization to death or the date of last contact. In the planned interim analysis, the primary efficacy analysis (primary study aim) was performed with all 172 patients (Intention to treat population, ITT population 1), Arm A including 87 patients, Arm B including 85 patients. The ITT population 1 includes all patients (172) who gave informed consent and who were randomized into one of the treatment arms at the time of the interim analysis.

End point type	Primary

End point timeframe:

Duration of trial

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[1]	85[2]		
Units: month				
median (confidence interval 95%)	9.6 (7.2 to 12.4)	12.0 (9.1 to 16.3)		

Notes:

[1] - Patients included in Arm A

[2] - Patients included in Arm B

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Paclitaxel/Topotecan v Cisplatin/Topotecan
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33
Method	Logrank

Secondary: 6 month PFS rate

End point title	6 month PFS rate

End point description:

Progression-free survival is the period from study entry until disease progression, death, or date of last contact.
In the final analysis at the end of the study, the secondary study aims were analyzed with all 173 patients (ITT population 2), Arm A including 88 patients, Arm B including 85 patients. The ITT population 2 includes all patients (173) who gave informed consent and who were randomized into one of the treatment arms during the whole study.

End point type	Secondary

End point timeframe:

Duration of trial

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	85		
Units: percent				
number (confidence interval 95%)	75.66 (71.73 to 79.59)	75.86 (72.20 to 79.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: 12 month PFS rate

End point title	12 month PFS rate

End point description:

In the final analysis at the end of the study, the secondary study aims were analyzed with all 173 patients (ITT population 2), Arm A including 88 patients, Arm B including 85 patients. The ITT population 2 includes all patients (173) who gave informed consent and who were randomized into one of the treatment arms during the whole study.

End point type	Secondary

End point timeframe:

Duration of trial

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	85		
Units: percent				
number (confidence interval 95%)	14 (8 to 24)	10 (5 to 19)		

Statistical analyses

No statistical analyses for this end point

Secondary: 24 month PFS rate

End point title	24 month PFS rate

End point description:

In the final analysis at the end of the study, the secondary study aims were analyzed with all 173 patients (ITT population 2), Arm A including 88 patients, Arm B including 85 patients. The ITT population 2 includes all patients (173) who gave informed consent and who were randomized into one of the treatment arms during the whole study.

End point type	Secondary

End point timeframe:

Duration of Trial

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	88	85		
Units: percent				
number (confidence interval 95%)	6 (3 to 15)	6 (2 to 15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response

End point title	Best overall response

End point description:

In the final analysis at the end of the study, the secondary study aims were analyzed with all 173 patients (ITT population 2), Arm A including 88 patients, Arm B including 85 patients. The ITT population 2 includes all patients (173) who gave informed consent and who were randomized into one of the treatment arms during the whole study.
Measurement of the longest dimension of each lesion size was required for follow-up. Change in the sum of these dimensions afforded some estimate of change in tumor size and, hence, of therapeutic efficacy. All assessments were made using the same techniques as were used for the baseline. These changes in an individual case had to be reported in terms of the best response achieved by that case since entering the study.

End point type	Secondary

End point timeframe:

Duration of trial

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[3]	67[4]		
Units: number of patients				
complete response	1	2		
partial remission	11	13		
stable disease	21	20		
progression	29	26		
symptomatic deterioration	3	6		
not evaluable	1	0		

Notes:

[3] - Only patients with at least one further tumor assessment since baseline were included.

[4] - Only patients with at least one further tumor assessment since baseline were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life

End point title	Quality of Life

End point description:

Association between treatment arm and cQOL was analyzed using linear mixed models with TOI as target variable. First, a linear mixed model was fitted with patient as random effect and treatment arm (categorical, Arm A vs Arm B), TOI before treatment (continuous), time (categorical; before chemotherapy cycle 2, before chemotherapy cycle 5, 9 months after randomization) and the interaction between treatment arm and time as fixed effect. Next, a linear mixed model with the same fixed effects but without the interaction term was fitted. Both models were compared using the likelihood ratio test. If the p value was significant, adjusted mean TOI in both treatment arms and the mean difference between treatment arms with corresponding 95% CI were estimated for each time point using the interaction model. Otherwise, respective overall mean TOI values were estimated using the reduced regression model. The models were fitted by maximum likelihood instead of of restricted maximuum likelihoood.

End point type	Secondary

End point timeframe:

before chemotherapy cycle 2, before chemotherapy cycle 5, 9 months after randomization

End point values	Paclitaxel/Topotecan	Cisplatin/Topotecan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[5]	38[6]		
Units: trial outcome index				
arithmetic mean (confidence interval 95%)	75.66 (71.73 to 79.59)	75.86 (72.20 to 79.53)		

Notes:

[5] - Patients with TOI information before chemotherapy and at least one followup TOI assessment.

[6] - Patients with TOI information before chemotherapy and at least one followup TOI assessment.

Statistical analyses

Statistical analysis title	Quality of life
Comparison groups	Paclitaxel/Topotecan v Cisplatin/Topotecan
Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.9
Method	Likelzhood ratio test
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	5.09

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The investigator must report all AEs occurring during the clinical study or within 30 days after administration of the last dose of the study drug, regardless of causality.

Adverse event reporting additional description:

The safety evaluation was performed in all randomized patients who were treated with at least one cycle of chemotherapy (n=161 (Safety Population); Arm A (Paclitaxel and Topotecan) 83 patients and Arm B (control group; Topotecan and Cisplatin) 78 patients).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Arm A (Paclitaxel and Topotecan)
Reporting group description: -	
Reporting group title	Arm B (Topotecan and Cisplatin)

Reporting group description: -

Serious adverse events	Arm A (Paclitaxel and Topotecan)	Arm B (Topotecan and Cisplatin)	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 83 (44.58%)	23 / 78 (29.49%)	
number of deaths (all causes)	65	61	
number of deaths resulting from adverse events	7	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Surgical and medical procedures			
Nephrostomy tube removal			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (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	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	8 / 83 (9.64%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal fistula			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 83 (3.61%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	2 / 83 (2.41%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	2 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	4 / 83 (4.82%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	3 / 6	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Sinus tachycardia			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Polyneuropathy in malignant disease			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 83 (10.84%)	5 / 78 (6.41%)	
occurrences causally related to treatment / all	8 / 14	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 83 (1.20%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 83 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 83 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 83 (1.20%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incontinence			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
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			
Arthralgia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (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			
Bacterial diarrhoea			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 83 (0.00%)	3 / 78 (3.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter colitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Arm A (Paclitaxel and Topotecan)	Arm B (Topotecan and Cisplatin)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 83 (100.00%)	77 / 78 (98.72%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 83 (1.20%)	6 / 78 (7.69%)	
occurrences (all)	1	9	
Tumour associated fever			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Cancer pain			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Hypertension			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	4	
Lymphoedema			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	2	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Deep vein thrombosis			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	7	
Hot flush			
subjects affected / exposed	2 / 83 (2.41%)	4 / 78 (5.13%)	
occurrences (all)	2	15	
Venous thrombosis limb			

subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Chest discomfort			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	3	
Fatigue			
subjects affected / exposed	59 / 83 (71.08%)	59 / 78 (75.64%)	
occurrences (all)	155	181	
Hernia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Mucosal dryness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Oedema			
subjects affected / exposed	34 / 83 (40.96%)	22 / 78 (28.21%)	
occurrences (all)	86	50	
Pain			
subjects affected / exposed	5 / 83 (6.02%)	8 / 78 (10.26%)	
occurrences (all)	6	23	
Peripheral swelling			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	9 / 83 (10.84%)	4 / 78 (5.13%)	
occurrences (all)	11	6	
Social circumstances			
Rash			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Breast disorder female			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Breast pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	3	1	
Vaginal discharge			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	3	
Vaginal haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	2	
Female genital tract fistula			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Perineal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Genital lesion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	3	0	
Vaginal fistula			

subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	3	
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Vulvovaginal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 83 (3.61%)	2 / 78 (2.56%)	
occurrences (all)	4	3	
Dyspnoea			
subjects affected / exposed	24 / 83 (28.92%)	16 / 78 (20.51%)	
occurrences (all)	46	42	
Epistaxis			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	2	2	
Pleural effusion			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Larynx irritation			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Insomnia			

subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 83 (30.12%)	21 / 78 (26.92%)	
occurrences (all)	61	37	
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 83 (26.51%)	22 / 78 (28.21%)	
occurrences (all)	36	38	
Blood bilirubin increased			
subjects affected / exposed	7 / 83 (8.43%)	6 / 78 (7.69%)	
occurrences (all)	9	9	
Blood calcium decreased			
subjects affected / exposed	21 / 83 (25.30%)	31 / 78 (39.74%)	
occurrences (all)	37	48	
Blood calcium increased			
subjects affected / exposed	7 / 83 (8.43%)	2 / 78 (2.56%)	
occurrences (all)	10	48	
Blood creatinine increased			
subjects affected / exposed	25 / 83 (30.12%)	24 / 78 (30.77%)	
occurrences (all)	50	75	
Blood lactate dehydrogenase increased			
subjects affected / exposed	37 / 83 (44.58%)	36 / 78 (46.15%)	
occurrences (all)	84	83	
Blood magnesium decreased			
subjects affected / exposed	23 / 83 (27.71%)	35 / 78 (44.87%)	
occurrences (all)	33	77	
Blood magnesium increased			
subjects affected / exposed	3 / 83 (3.61%)	4 / 78 (5.13%)	
occurrences (all)	3	4	
Blood potassium decreased			

subjects affected / exposed	20 / 83 (24.10%)	18 / 78 (23.08%)	
occurrences (all)	28	27	
Blood potassium increased			
subjects affected / exposed	17 / 83 (20.48%)	15 / 78 (19.23%)	
occurrences (all)	20	26	
Blood sodium decreased			
subjects affected / exposed	19 / 83 (22.89%)	23 / 78 (29.49%)	
occurrences (all)	22	45	
Blood sodium increased			
subjects affected / exposed	4 / 83 (4.82%)	5 / 78 (6.41%)	
occurrences (all)	4	7	
Body temperature increased			
subjects affected / exposed	4 / 83 (4.82%)	6 / 78 (7.69%)	
occurrences (all)	4	9	
Creatinine renal clearance increased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	51 / 83 (61.45%)	52 / 78 (66.67%)	
occurrences (all)	133	169	
Weight decreased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Blood phosphorus increased			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Transaminases increased			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
General physical condition abnormal			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	36 / 83 (43.37%)	36 / 78 (46.15%)	
occurrences (all)	87	92	

Urine analysis abnormal			
subjects affected / exposed	38 / 83 (45.78%)	39 / 78 (50.00%)	
occurrences (all)	75	74	
Injury, poisoning and procedural complications			
Radius fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardiovascular disorder			
subjects affected / exposed	6 / 83 (7.23%)	3 / 78 (3.85%)	
occurrences (all)	9	4	
Sinus tachycardia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Ageusia			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	2	2	
Dizzines			
subjects affected / exposed	3 / 83 (3.61%)	3 / 78 (3.85%)	
occurrences (all)	4	6	
Dysaesthesia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Dysarthria			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 83 (3.61%)	5 / 78 (6.41%)	
occurrences (all)	4	7	

Monoparesis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Neurotoxicity			
subjects affected / exposed	35 / 83 (42.17%)	21 / 78 (26.92%)	
occurrences (all)	100	49	
Polyneuropathy in malignant disease			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	2	
Sciatica			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Radicular syndrome			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	82 / 83 (98.80%)	76 / 78 (97.44%)	
occurrences (all)	1075	832	
Febrile neutropenia			
subjects affected / exposed	3 / 83 (3.61%)	4 / 78 (5.13%)	
occurrences (all)	3	4	
Leukopenia			
subjects affected / exposed	64 / 83 (77.11%)	74 / 78 (94.87%)	
occurrences (all)	381	468	
Neutropenia			
subjects affected / exposed	45 / 83 (54.22%)	61 / 78 (78.21%)	
occurrences (all)	117	264	
Pancytopenia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	23 / 83 (27.71%)	55 / 78 (70.51%)	
occurrences (all)	60	243	
Ear and labyrinth disorders			

Deafness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Ototoxicity			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Eye disorders			
Eye pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 83 (1.20%)	8 / 78 (10.26%)	
occurrences (all)	6	9	
Abdominal pain lower			
subjects affected / exposed	7 / 83 (8.43%)	6 / 78 (7.69%)	
occurrences (all)	8	11	
Abdominal pain upper			
subjects affected / exposed	2 / 83 (2.41%)	5 / 78 (6.41%)	
occurrences (all)	2	5	
Ascites			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Colitis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Constipation			

subjects affected / exposed	27 / 83 (32.53%)	33 / 78 (42.31%)	
occurrences (all)	43	68	
Diarrhoea			
subjects affected / exposed	30 / 83 (36.14%)	26 / 78 (33.33%)	
occurrences (all)	51	49	
Dry mouth			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	2	
Gastric haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 83 (2.41%)	3 / 78 (3.85%)	
occurrences (all)	3	4	
Gastrointestinal pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Ileus			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	35 / 83 (42.17%)	52 / 78 (66.67%)	
occurrences (all)	78	134	
Rectal haemorrhage			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Stomatitis			

subjects affected / exposed	15 / 83 (18.07%)	13 / 78 (16.67%)	
occurrences (all)	26	23	
Vomiting			
subjects affected / exposed	22 / 83 (26.51%)	29 / 78 (37.18%)	
occurrences (all)	36	56	
Subileus			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Dyschezia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Enterocutaneous fistula			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Tooth pulp haemorrhage			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Bile duct obstruction			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	58 / 83 (69.88%)	53 / 78 (67.95%)	
occurrences (all)	69	196	
Dry skin			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Neurodermatitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Night sweats			

subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	4	
Skin hyperpigmentation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Nail pigmentation			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	4	2	
Renal and urinary disorders			
Bladder discomfort			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Bladder pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	0 / 83 (0.00%)	2 / 78 (2.56%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	4 / 83 (4.82%)	1 / 78 (1.28%)	
occurrences (all)	6	1	
Hydronephrosis			
subjects affected / exposed	2 / 83 (2.41%)	1 / 78 (1.28%)	
occurrences (all)	2	1	
Incontinence			

subjects affected / exposed	3 / 83 (3.61%)	0 / 78 (0.00%)	
occurrences (all)	7	0	
Nocturia			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Pollakiuria			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Renal disorder			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Renal pain			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Urine abnormality			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Urogenital fistula			
subjects affected / exposed	1 / 83 (1.20%)	1 / 78 (1.28%)	
occurrences (all)	1	1	
Urinary tract obstruction			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	1	2	
Urinary tract pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Stress urinary incontinence			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Urinary tract discomfort			
subjects affected / exposed	2 / 83 (2.41%)	0 / 78 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	15 / 83 (18.07%)	16 / 78 (20.51%)	
occurrences (all)	18	23	
Back pain			
subjects affected / exposed	3 / 83 (3.61%)	2 / 78 (2.56%)	
occurrences (all)	6	4	
Bone pain			
subjects affected / exposed	2 / 83 (2.41%)	2 / 78 (2.56%)	
occurrences (all)	8	2	
Myalgia			
subjects affected / exposed	15 / 83 (18.07%)	12 / 78 (15.38%)	
occurrences (all)	24	22	
Neck pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	5	0	
Pain in extremity			
subjects affected / exposed	4 / 83 (4.82%)	3 / 78 (3.85%)	
occurrences (all)	5	5	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	5 / 83 (6.02%)	4 / 78 (5.13%)	
occurrences (all)	7	8	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	7 / 83 (8.43%)	5 / 78 (6.41%)	
occurrences (all)	8	5	
Erysipelas			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Fungal skin infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	3	0	
Gastroenteritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Herpes simplex			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	17 / 83 (20.48%)	15 / 78 (19.23%)	
occurrences (all)	21	17	
Influenza			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Rash pustular			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 83 (3.61%)	2 / 78 (2.56%)	
occurrences (all)	4	3	
Urethritis			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 83 (2.41%)	2 / 78 (2.56%)	
occurrences (all)	2	4	
Vulvitis			

subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Urosepsis			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Vascular access site infection			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 83 (0.00%)	1 / 78 (1.28%)	
occurrences (all)	0	1	
Weight fluctuation			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	1 / 83 (1.20%)	0 / 78 (0.00%)	
occurrences (all)	1	0	
Decreased appetite			
subjects affected / exposed	1 / 83 (1.20%)	2 / 78 (2.56%)	
occurrences (all)	2	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2011	After a 2-year extension of the recruitment period and slow recruitment (172 of 312 planed patients) an amendment of the study protocol (Amendment 1; protocol Version 2) was accepted by the IEC to perform an interim analysis, to check if a continuation of the study could answer the primary objective (difference in overall survival). An adaptive interim analysis (AIA) was performed on February 27th 2012. The AIA allows sample size re-calculation for the second stage of the trial after the interim analysis or, if the case may be, early stopping of the trial after the interim analysis. In the first case, a final p-value is calculated from the p-values of both stages. In the second case, the p-value of the interim analysis is the p-value of the primary objective. The following parameters were selected for the planning of the two phases of the study (first phase up to AIA, second phase after AIA: a global α = 0.05 (two-sided) and the total power of 80%. Let p1 be the p-value for the statistical test of the interim analysis. α0 = 0.5 was the critical lower limit, so that for p1 ≥ α0, the interim analysis would lead to early stopping with the acceptance of the null hypothesis ("no treatment effect"). One would also stop if a treatment difference has been estimated that does not indicate the intended direction. α1 = 0.0233 was critical upper limit, so that for p1 < α1 the interim analysis would stop with the rejection of the null hypothesis. If p1 was between α1 and α0 and the estimated treatment difference indicates the intended direction, a second study phase would be planned. The interim analysis revealed no significant difference in overall survival rates, but a trend toward superiority of the control group (Arm B). From a statistical perspective, continuing recruitment to demonstrate superiority of arm A was not reasonable; therefore, recruitment was terminated after the interim analysis. Patients were allowed to continue trial therapy that had already been started.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
31 December 2012	Recriutment was stopped on 31-Sec-20111 for preparation of an interim analysis. The interim analysis perfomred on 27-Apr-2012 revealed no significant difference in overall survival rates, but a trend toward superiority of the control group (Arm B). From a statistical perspective, continuing recruitment to demonstrate superiority of arm A was not reasonable; therefore, recruitment was terminated after the interim analysis. At the same time, since there were no safety concerns identified from the safety report, patients were allowed to continue effective therapy that had already been started.	-

Notes:

Limitations and caveats

None reported