Clinical trial results:
A randomized, double-blind, placebo controlled, multicenter, phase II study of adding AMG 479, a fully human monoclonal antibody against insulin-like growth factor type 1 receptor (IGF-1R) to first line chemotherapy in patients with optimally debulked (< 1cm) epithelial ovarian cancer.

Summary

EudraCT number	2008-001551-22
Trial protocol	FR DE ES IE GB
Global end of trial date	07 November 2014

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	TRIO 014

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00718523
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Translational Research In Oncology (TRIO)
Sponsor organisation address	Suite 1100, 9925-109th Street, Edmonton , Canada, T5K2J8
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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	06 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2013
Global end of trial reached?	Yes
Global end of trial date	07 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate whether the addition of AMG 479 to paclitaxel and carboplatin chemotherapy improves progression free survival (PFS) when compared to paclitaxel and carboplatin chemotherapy alone.

Protection of trial subjects:

The clinical trial was conducted in accordance with the recommendation of the Declaration of Helsinki (Helsinki 1964 as amended) and with the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). The study also complied with the laws and regulations, as well as any applicable guidelines of the countries where the study was conducted. A Data Monitoring Committee (DMC) was appointed for this trial.

Background therapy:

Paclitaxel
Carboplatin

Evidence for comparator: -

Actual start date of recruitment	30 January 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	4 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 82
Country: Number of subjects enrolled	United States: 59
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Israel: 4
Worldwide total number of subjects	170
EEA total number of subjects	97

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)	120
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted over a total of 55 sites in 8 countries.

Pre-assignment

Screening details:

Female, 18 years of age/older/legal age with optimally debulked (<1 cm) FIGO stage III and IV (positive pleural cytology only) ovarian epithelial carcinoma. ECOG performance status ≤ 2, non diabetics patients type 1 or 2, adequate coagulation parameters, INR≤1,5 and prothrombin time or (activated) partial thromboplastin time ≤ 1,5 ULN.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Placebo plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of placebo administered on Day 1 of each 21-day cycle.

Arm type	Placebo
Investigational medicinal product name	AMG 479 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AMG 479 placebo: matching placebo administered Day 1 of each 21 day cycle

Arm title	Experimental

Arm description:

AMG 479 plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of AMG 479 single agent administered on Day 1 of each 21-day cycle

Arm type	Experimental
Investigational medicinal product name	AMG 479
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

AMG 479: solution for infusion - 18 mg/kg on day 1 of each 21-day cycle

Number of subjects in period 1	Control	Experimental
Started	84	86
Completed	66	62
Not completed	18	24
Adverse event, serious fatal	13	17
Consent withdrawn by subject	5	7

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
Placebo plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of placebo administered on Day 1 of each 21-day cycle.	
Reporting group title	Experimental
Reporting group description:	
AMG 479 plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of AMG 479 single agent administered on Day 1 of each 21-day cycle	

Reporting group values	Control	Experimental	Total
Number of subjects	84	86	170
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	59	61	120
From 65-84 years	25	25	50
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.1	57.2	
standard deviation	± 10	± 12.3	-
Gender categorical Units: Subjects			
Female	84	86	170
Male	0	0	0
Region of enrollment Units: Subjects			
United States	25	34	59
United Kingdom	1	2	3
Canada	4	6	10
France	7	3	10
Israel	2	2	4
Spain	1	1	2
Germany	44	38	82
Eastern Cooperative Oncology Group Performance Status Units: Subjects			
PS 0 (fully active)	36	32	68
PS 1 (restricted in physically strenuous activity)	43	46	89

PS 2 (ambulatory and capable of all selfcare)	5	6	11
Missing	0	2	2
Origin of tumor Units: Subjects			
Primary peritoneal	8	4	12
Fallopian tube	4	4	8
Ovarian	69	77	146
Ovarian + Primary peritoneal	0	1	1
Ovarian + Fallopian tube	2	0	2
Missing	1	0	1
Stage at first diagnosis (International Federation of Gynecology and Obstetrics (FIGO)) Units: Subjects			
IIIA	3	2	5
IIIB	10	6	16
IIIC	65	72	137
IV	6	6	12
Histopathologic type Units: Subjects			
papillary serous	69	72	141
mucinous	0	1	1
endometroid	4	5	9
clear cell	2	2	4
mixed	5	3	8
other	4	3	7
Histologic Grade Units: Subjects			
G1 (well differentiated)	1	5	6
G2 (moderately differentiated)	15	18	33
G3 (poorly differentiated)	65	57	122
Not done	3	6	9
Number of prior therapies Units: Subjects			
1 therapy	80	78	158
2 therapies	4	8	12
CA 125 status Units: Subjects			
with elevated CA 125	67	70	137
with CA 125 in the normal range	17	15	32
missing	0	1	1
Time from surgery to first treatment dose Units: weeks			
arithmetic mean	5.1	5.1	
standard deviation	± 1.2	± 1.4	-
Time from diagnosis to randomization Units: weeks			
arithmetic mean	5.2	5.4	
standard deviation	± 2.3	± 3.4	-

Subject analysis sets

Subject analysis set title	Intent To treat Population (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients randomized in the study regardless whether they actually received treatment or not. Patients were analyzed according to their treatment arm at randomization.

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

Subject analysis set description:

The safety population consisted of all treated patients who received at least one dose of study treatment. Patients were analyzed according to the treatment actually received.

Reporting group values	Intent To treat Population (ITT)	Safety Population	
Number of subjects	170	165	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	120	115	
From 65-84 years	50	50	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	57.6	57.6	
standard deviation	± 11.2	± 11.4	
Gender categorical Units: Subjects			
Female	170	165	
Male	0	0	
Region of enrollment Units: Subjects			
United States	59		
United Kingdom	3		
Canada	10		
France	10		
Israel	4		
Spain	2		
Germany	82		
Eastern Cooperative Oncology Group Performance Status Units: Subjects			
PS 0 (fully active)	68	67	
PS 1 (restricted in physically strenuous activity)	89	87	
PS 2 (ambulatory and capable of all selfcare)	11	9	
Missing	2	2	

Origin of tumor Units: Subjects			
Primary peritoneal	12	12	
Fallopian tube	8	7	
Ovarian	146	142	
Ovarian + Primary peritoneal	1	1	
Ovarian + Fallopian tube	2	2	
Missing	1	1	
Stage at first diagnosis (International Federation of Gynecology and Obstetrics (FIGO)) Units: Subjects			
IIIA	5	4	
IIIB	16	16	
IIIC	137	134	
IV	12	11	
Histopathologic type Units: Subjects			
papillary serous	141	137	
mucinous	1	1	
endometroid	9	9	
clear cell	4	4	
mixed	8	7	
other	7	7	
Histologic Grade Units: Subjects			
G1 (well differentiated)	6	6	
G2 (moderately differentiated)	33	33	
G3 (poorly differentiated)	122	117	
Not done	9	9	
Number of prior therapies Units: Subjects			
1 therapy	158	153	
2 therapies	12	12	
CA 125 status Units: Subjects			
with elevated CA 125	137	132	
with CA 125 in the normal range	32	32	
missing	1	1	
Time from surgery to first treatment dose Units: weeks			
arithmetic mean	5.1	5.1	
standard deviation	± 1.3	± 1.3	
Time from diagnosis to randomization Units: weeks			
arithmetic mean	5.3	5.3	
standard deviation	± 2.9	± 3	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Placebo plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of placebo administered on Day 1 of each 21-day cycle.	
Reporting group title	Experimental
Reporting group description:	
AMG 479 plus paclitaxel/carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of AMG 479 single agent administered on Day 1 of each 21-day cycle	
Subject analysis set title	Intent To treat Population (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients randomized in the study regardless whether they actually received treatment or not. Patients were analyzed according to their treatment arm at randomization.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population consisted of all treated patients who received at least one dose of study treatment. Patients were analyzed according to the treatment actually received.	

Primary: Progression Free Survival (PFS): Time from Randomization until date of Progression or Death

End point title	Progression Free Survival (PFS): Time from Randomization until date of Progression or Death
End point description:	
A patient may have been declared to have progressive disease on the basis of radiological measurement of tumor lesions assessment or CA125 evaluation (tumor measuremts taking precedence). Radiological progression was defined as per the RECIST guidelines (Therasse et al, JNCI2000) as at least 20% increase in the sum of the longest diameters of target lesions (ref the smallest sum of the longest diam recorded since the treatmt started or since the appearance of at least 1 new lesion). Serum CA125 progression was defined, according to the 2005 GCIG def: patients with: -elevated CA125 pretreatmt and normalization of CA125 has to show evidence of CA125 ≥ 2 X the upper normal limit on 2 occasions at least 1 wk apart OR -elevated CA125 pretreatmt which never normalized must show evidence of CA125 ≥ 2 X the nadir value on 2 occasions at least 1 wk apart OR -CA125 in the normal range pretreatment had to show evidence of CA125 ≥ 2 X the upper normal limit on 2 occasions at least 1 wk apart.	
End point type	Primary
End point timeframe:	
Radiological tumor assessment: every 12 (+ /- 1) weeks for 3 years after randomization + CA 125: day 1 of each cycle	

End point values	Control	Experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	86		
Units: Months				
median (confidence interval 95%)				
Progression Free Survival (PFS)	16.69 (14.686 to 28.123)	15.737 (12.09 to 21.388)		

Statistical analyses

Statistical analysis title	Kaplan Meier

Statistical analysis description:

To estimate whether the addition of AMG 479 to paclitaxel and carboplatin chemotherapy improves progression free survival (PFS) when compared to paclitaxel and carboplatin chemotherapy alone.

Comparison groups	Control v Experimental
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.338
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.215
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.813
upper limit	1.816

Notes:

[1] - The study is designed to provide evidence to either support the null hypothesis H0: λ equals 1 or to reject it in favor of the alternative hypothesis HA: λ does not equal 1, where λ is the hazard ratio for PFS: experimental arm/control arm.

However, the study is designed to primarily demonstrate activity and feasibility of AMG 479 in combination with paclitaxel/carboplatin in ovarian cancer, rather than to provide statistical power to support a new standard regimen.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The monitoring period for AEs started from signature of the ICF and continued up to 30 days after last dose.

Adverse event reporting additional description:

The participant flow module is based on the ITT population, so patients are counted according to their "randomization group". For "participants at risk", patients are grouped by their "actual treatment"; 4 patients were allocated with incorrect treatment and received AMG 479 instead of placebo. The total number of patients treated remains the same.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	UN

Reporting groups

Reporting group title	Arm I

Reporting group description:

Placebo plus paclitaxel/carboplatin administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of placebo administered on Day 1 of each 21-day cycle.

AMG479 Placebo: matching placebo administered Day 1 of each 21 day cycle.

There were 13 deaths in total with 1 resulting from a serious adverse event (convulsion).

4 patients radomized to recieve placebo actually received AMG 479.

Reporting group title	Arm II

Reporting group description:

AMG 479 plus paclitaxel:carboplatin chemotherapy administered on Day 1 of each 21-day cycle for 6 cycles - then 6 additional cycles of AMG 479 single agent administered on Day 1 of each 21-day cycle.

AMG 479: solution for infusion - 18 mg/kg on day 1 of each 21-day cycle.

There were 17 deaths reported in this group, with 2 patient deaths resulting from serious adverse events - UNRELATED TO TREATMENT (1 patient death resulting from aortic aneurysm, and the other patient death resulting from intestinal infarction AND haemorrhage intracranial combined).

Serious adverse events	Arm I	Arm II	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 77 (40.26%)	30 / 88 (34.09%)	
number of deaths (all causes)	13	17	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphocele			

subjects affected / exposed	2 / 77 (2.60%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (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			
Intestinal infarction	Additional description: One patient died resulting from 2 events: intracranial hemorrhage AND intestinal infarction. Both events were possibly caused by ovarian cancer and hypertension but NOT related to treatment.		
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 77 (1.30%)	5 / 88 (5.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 77 (2.60%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			

subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 77 (3.90%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	2 / 77 (2.60%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			

subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion	Additional description: Patient in the placebo group died due to convulsion. The event was determined as possibly related to disease progression but NOT related to treatment.		
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial	Additional description: One patient died resulting from 2 events: intracranial hemorrhage AND intestinal infarction. Both events were possibly caused by ovarian cancer and hypertension but NOT related to treatment.		
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorder			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (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	1 / 77 (1.30%)	6 / 88 (6.82%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukopenia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 77 (1.30%)	5 / 88 (5.68%)	
occurrences causally related to treatment / all	0 / 1	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal pain			
subjects affected / exposed	2 / 77 (2.60%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (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	2 / 77 (2.60%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 77 (2.60%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rheumatoid arthritis			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 77 (0.00%)	3 / 88 (3.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 77 (1.30%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (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	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 77 (0.00%)	2 / 88 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
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 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 77 (1.30%)	0 / 88 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			

subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 77 (0.00%)	1 / 88 (1.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm I	Arm II	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 77 (100.00%)	86 / 88 (97.73%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	13 / 77 (16.88%)	7 / 88 (7.95%)	
occurrences (all)	13	8	
Hypertension			
subjects affected / exposed	3 / 77 (3.90%)	6 / 88 (6.82%)	
occurrences (all)	3	6	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 77 (11.69%)	5 / 88 (5.68%)	
occurrences (all)	17	6	
Chills			
subjects affected / exposed	4 / 77 (5.19%)	10 / 88 (11.36%)	
occurrences (all)	4	12	
Fatigue			
subjects affected / exposed	46 / 77 (59.74%)	49 / 88 (55.68%)	
occurrences (all)	55	55	

Oedema peripheral			
subjects affected / exposed	8 / 77 (10.39%)	5 / 88 (5.68%)	
occurrences (all)	8	5	
Pain			
subjects affected / exposed	9 / 77 (11.69%)	11 / 88 (12.50%)	
occurrences (all)	10	11	
Pyrexia			
subjects affected / exposed	13 / 77 (16.88%)	9 / 88 (10.23%)	
occurrences (all)	15	12	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	10 / 77 (12.99%)	8 / 88 (9.09%)	
occurrences (all)	14	10	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 77 (9.09%)	9 / 88 (10.23%)	
occurrences (all)	7	9	
Dyspnoea			
subjects affected / exposed	15 / 77 (19.48%)	12 / 88 (13.64%)	
occurrences (all)	15	12	
Epistaxis			
subjects affected / exposed	6 / 77 (7.79%)	12 / 88 (13.64%)	
occurrences (all)	6	13	
Oropharyngeal pain			
subjects affected / exposed	5 / 77 (6.49%)	4 / 88 (4.55%)	
occurrences (all)	5	4	
Rhinorrhoea			
subjects affected / exposed	4 / 77 (5.19%)	3 / 88 (3.41%)	
occurrences (all)	4	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 77 (5.19%)	2 / 88 (2.27%)	
occurrences (all)	4	2	
Depression			
subjects affected / exposed	6 / 77 (7.79%)	2 / 88 (2.27%)	
occurrences (all)	6	2	

Insomnia			
subjects affected / exposed	6 / 77 (7.79%)	7 / 88 (7.95%)	
occurrences (all)	6	7	
Investigations			
Weight increased			
subjects affected / exposed	2 / 77 (2.60%)	5 / 88 (5.68%)	
occurrences (all)	2	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	15 / 77 (19.48%)	9 / 88 (10.23%)	
occurrences (all)	16	9	
Dysgueusia			
subjects affected / exposed	15 / 77 (19.48%)	15 / 88 (17.05%)	
occurrences (all)	17	16	
Headache			
subjects affected / exposed	15 / 77 (19.48%)	23 / 88 (26.14%)	
occurrences (all)	17	30	
Neuropathy peripheral			
subjects affected / exposed	15 / 77 (19.48%)	24 / 88 (27.27%)	
occurrences (all)	17	25	
Paraesthesia			
subjects affected / exposed	7 / 77 (9.09%)	3 / 88 (3.41%)	
occurrences (all)	9	3	
Peripheral sensory neuropathy			
subjects affected / exposed	32 / 77 (41.56%)	27 / 88 (30.68%)	
occurrences (all)	35	31	
Polyneuropathy			
subjects affected / exposed	11 / 77 (14.29%)	8 / 88 (9.09%)	
occurrences (all)	11	8	
Syncope			
subjects affected / exposed	4 / 77 (5.19%)	1 / 88 (1.14%)	
occurrences (all)	4	1	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 77 (5.19%)	3 / 88 (3.41%)	
occurrences (all)	4	3	
Vertigo			

subjects affected / exposed	4 / 77 (5.19%)	8 / 88 (9.09%)	
occurrences (all)	4	8	
Eye disorders			
Vision blurred			
subjects affected / exposed	4 / 77 (5.19%)	4 / 88 (4.55%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	16 / 77 (20.78%)	18 / 88 (20.45%)	
occurrences (all)	16	22	
Abdominal pain upper			
subjects affected / exposed	14 / 77 (18.18%)	6 / 88 (6.82%)	
occurrences (all)	16	6	
Constipation			
subjects affected / exposed	28 / 77 (36.36%)	28 / 88 (31.82%)	
occurrences (all)	33	32	
Diarrhoea			
subjects affected / exposed	24 / 77 (31.17%)	37 / 88 (42.05%)	
occurrences (all)	32	45	
Dry mouth			
subjects affected / exposed	6 / 77 (7.79%)	11 / 88 (12.50%)	
occurrences (all)	6	13	
Nausea			
subjects affected / exposed	51 / 77 (66.23%)	46 / 88 (52.27%)	
occurrences (all)	67	53	
Stomatitis			
subjects affected / exposed	17 / 77 (22.08%)	24 / 88 (27.27%)	
occurrences (all)	19	25	
Vomiting			
subjects affected / exposed	31 / 77 (40.26%)	29 / 88 (32.95%)	
occurrences (all)	38	32	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 77 (1.30%)	5 / 88 (5.68%)	
occurrences (all)	1	6	
Alopecia			

subjects affected / exposed	68 / 77 (88.31%)	66 / 88 (75.00%)	
occurrences (all)	68	66	
Dry skin			
subjects affected / exposed	3 / 77 (3.90%)	5 / 88 (5.68%)	
occurrences (all)	3	5	
Nail disorder			
subjects affected / exposed	2 / 77 (2.60%)	8 / 88 (9.09%)	
occurrences (all)	2	8	
Pruritus			
subjects affected / exposed	11 / 77 (14.29%)	11 / 88 (12.50%)	
occurrences (all)	15	12	
Rash			
subjects affected / exposed	17 / 77 (22.08%)	24 / 88 (27.27%)	
occurrences (all)	22	28	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	24 / 77 (31.17%)	30 / 88 (34.09%)	
occurrences (all)	39	34	
Back pain			
subjects affected / exposed	14 / 77 (18.18%)	8 / 88 (9.09%)	
occurrences (all)	16	8	
Bone pain			
subjects affected / exposed	13 / 77 (16.88%)	18 / 88 (20.45%)	
occurrences (all)	15	21	
Muscle spasms			
subjects affected / exposed	2 / 77 (2.60%)	6 / 88 (6.82%)	
occurrences (all)	2	6	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 77 (5.19%)	0 / 88 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal pain			
subjects affected / exposed	5 / 77 (6.49%)	3 / 88 (3.41%)	
occurrences (all)	6	3	
Myalgia			

subjects affected / exposed	20 / 77 (25.97%)	27 / 88 (30.68%)	
occurrences (all)	26	33	
Pain in extremity			
subjects affected / exposed	16 / 77 (20.78%)	11 / 88 (12.50%)	
occurrences (all)	17	13	
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 77 (6.49%)	2 / 88 (2.27%)	
occurrences (all)	5	2	
Cystitis			
subjects affected / exposed	5 / 77 (6.49%)	2 / 88 (2.27%)	
occurrences (all)	9	2	
Nasopharyngitis			
subjects affected / exposed	12 / 77 (15.58%)	7 / 88 (7.95%)	
occurrences (all)	13	10	
Urinary tract infection			
subjects affected / exposed	11 / 77 (14.29%)	7 / 88 (7.95%)	
occurrences (all)	15	8	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 77 (20.78%)	12 / 88 (13.64%)	
occurrences (all)	17	14	
Hypomagnesaemia			
subjects affected / exposed	2 / 77 (2.60%)	5 / 88 (5.68%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 January 2009	Correction of typography regarding a time of intensive PK sampling: to be read at 4hours post-infusion instead of 6hours post-infusion. Extension of the rule for withdrawing a patient under stable anticoagulation treatment but suffering of concurrent thrombocytopenia.
02 April 2010	Adding the audiometry assessment; Adjustment in carboplatin doses; Update of guidelines for treatment modifications; Clarification on timing of study procedures.
07 September 2011	Update in company name; Removal of central reading of images; Decrease in the follow up period; Clarification on eligibility criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported