Clinical trial results:
Capecitabine and bevacizumab ± vinorelbine as 1st line treatment in HER2/neu-negative metastatic or locally advanced inoperable breast cancer patients

Summary

EudraCT number	2008-003779-37
Trial protocol	DE
Global end of trial date	15 January 2016

Results information

Result version number	v1 (current)
This version publication date	04 August 2021
First version publication date	04 August 2021
Summary attachment (see zip file)	CARIN Study Results (CARIN_CSR_E3_Synopsis_v2.0_17Okt2016.pdf)

Trial information

Trial identification

Sponsor protocol code	IOM-080-2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00868634
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	iOMEDICO AG
Sponsor organisation address	Ellen-Gottlieb-Str. 19, Freiburg, Germany, 79106
Public contact	Clinical Trials Information, iOMEDICO AG, 0049 761152420, info@iomedico.com
Scientific contact	Clinical Trials Information, iOMEDICO AG, 0049 761152420, info@iomedico.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 October 2015
Global end of trial reached?	Yes
Global end of trial date	15 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To verify the superiority of the combination capecitabine, bevacizumab and vinorelbin compared to the combination of capecitabine and bevacizumab.
Primary endpoint: Progression free survival

Protection of trial subjects:

Independent ethics committees at all participating sites approved the protocol and all modifications. All patients provided written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 592
Worldwide total number of subjects	592
EEA total number of subjects	592

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)	355
From 65 to 84 years	237
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment 1:1

Pre-assignment

Screening details:

After a patient had signed informed consent form, screening procedures for study enrollment were completed.

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	Arm A - CAP/BEV

Arm description:

Capecitabine + bevacizumab

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 (twice daily, days 1-14, q3w)

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

15 mg/kg (day 1, q3w)

Arm title	Arm B - CAP/BEV/VIN

Arm description:

Capecitabine + bevacizumab + vinorelbine

Arm type	Experimental
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1000 mg/m2 (twice daily, days 1-14, q3w)

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use
Dosage and administration details: 15 mg/kg (day 1, q3w)	
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 25 mg/m2 (days 1+8, q3w)	

Number of subjects in period 1	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN
Started	297	295
Completed	297	295

Baseline characteristics

Reporting groups	
Reporting group title	Arm A - CAP/BEV
Reporting group description: Capecitabine + bevacizumab	
Reporting group title	Arm B - CAP/BEV/VIN
Reporting group description: Capecitabine + bevacizumab + vinorelbine	

Reporting group values	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN	Total
Number of subjects	297	295	592
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)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
< 65 years	192	163	355
>= 65 years	105	132	237
Gender categorical Units: Subjects			
Female	297	295	592

End points

End points reporting groups	
Reporting group title	Arm A - CAP/BEV
Reporting group description: Capecitabine + bevacizumab	
Reporting group title	Arm B - CAP/BEV/VIN
Reporting group description: Capecitabine + bevacizumab + vinorelbine	

Primary: PFS - Progression Free Survival	
End point title	PFS - Progression Free Survival
End point description:	
End point type	Primary
End point timeframe: Time from first randomizaton until first signs of tumor progression or death from any cause.	

End point values	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	295		
Units: months				
median (inter-quartile range (Q1-Q3))	8.8 (8.15 to 9.79)	9.6 (8.8 to 11.2)		

Statistical analyses

Statistical analysis title	Kaplan Meier Estimates
Comparison groups	Arm A - CAP/BEV v Arm B - CAP/BEV/VIN
Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.01
Variability estimate	Standard deviation

Secondary: ORR - Overall Response Rate

End point title	ORR - Overall Response Rate

End point description:

End point type	Secondary

End point timeframe:

Patients were considered evaluable for response if they had measurable disease at baseline

End point values	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	179[1]	162[2]		
Units: Number of patients	65	77		

Notes:

[1] - Only patients with measurable disease at baseline were evaluable

[2] - Only patients with measurable disease at baseline were evaluable

Statistical analyses

Statistical analysis title	ORR Analysis
Comparison groups	Arm A - CAP/BEV v Arm B - CAP/BEV/VIN
Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3986
upper limit	0.9936
Variability estimate	Standard deviation

Secondary: OS - Overall Survival

End point title	OS - Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Time from randomization until death

End point values	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	297	295		
Units: months				
median (inter-quartile range (Q1-Q3))	25.1 (23.06 to 28.98)	27.2 (23.46 to 29.67)		

Statistical analyses

Statistical analysis title	Kaplan Meier Estimates
Comparison groups	Arm A - CAP/BEV v Arm B - CAP/BEV/VIN
Number of subjects included in analysis	592
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	≤ 0.05
Method	Logrank
Parameter estimate	Average Hazard Ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.03
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE assessment started with randomization until end of treatment plus 30 days safety follow-up (=treatment emergent period)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Arm A - CAP/BEV
Reporting group description: -	
Reporting group title	Arm B - CAP/BEV/VIN

Reporting group description: -

Serious adverse events	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN	
Total subjects affected by serious adverse events			
subjects affected / exposed	112 / 297 (37.71%)	150 / 295 (50.85%)	
number of deaths (all causes)	219	205	
number of deaths resulting from adverse events	18	25	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to bone marrow			
subjects affected / exposed	2 / 297 (0.67%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to meninges			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to peritoneum			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Tumour pain			
subjects affected / exposed	2 / 297 (0.67%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 297 (0.34%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Haematoma			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	3 / 297 (1.01%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebosclerosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	2 / 297 (0.67%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	2 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 297 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Catheter management			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemotherapy			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiofrequency ablation of oesophagus			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (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			
Asthenia			
subjects affected / exposed	1 / 297 (0.34%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Chest pain			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	6 / 297 (2.02%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 6	1 / 4	
deaths causally related to treatment / all	0 / 4	1 / 3	
Fatigue			
subjects affected / exposed	0 / 297 (0.00%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 297 (2.02%)	14 / 295 (4.75%)	
occurrences causally related to treatment / all	2 / 6	7 / 15	
deaths causally related to treatment / all	0 / 1	1 / 4	
Impaired healing			

subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
multi-organ failure			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 297 (0.67%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ulcer			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	2 / 297 (0.67%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
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			
Aspiration			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 297 (2.02%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	1 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion			
subjects affected / exposed	2 / 297 (0.67%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 297 (0.34%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 297 (1.35%)	16 / 295 (5.42%)	
occurrences causally related to treatment / all	3 / 4	11 / 16	
deaths causally related to treatment / all	1 / 1	1 / 4	
Respiratory failure			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 297 (0.34%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure orthostatic abnormal			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Granulocyte count decreased			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein total decreased			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury corneal			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mitral valve incompetence			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic coma			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dizziness			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	2 / 297 (0.67%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic intolerance			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 297 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diplegia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 297 (0.34%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotoxicity			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
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 / 297 (0.34%)	20 / 295 (6.78%)	
occurrences causally related to treatment / all	1 / 1	26 / 26	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lymphadenopathy			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 297 (0.00%)	19 / 295 (6.44%)	
occurrences causally related to treatment / all	0 / 0	22 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	4 / 297 (1.35%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	3 / 4	3 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 297 (0.67%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 297 (0.34%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 297 (0.67%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 297 (0.00%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colitis			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 297 (0.67%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 297 (2.36%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	4 / 7	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enteritis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (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	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 297 (0.34%)	5 / 295 (1.69%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 297 (0.67%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 297 (1.01%)	6 / 295 (2.03%)	
occurrences causally related to treatment / all	2 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 297 (1.01%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (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			
Angioedema			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity vasculitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin fissures			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 297 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (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	0 / 297 (0.00%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Ureteric stenosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint effusion			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			

subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 297 (0.34%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Actinomycosis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amoebic dysentery			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial disease carrier			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			

subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 297 (0.67%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 297 (0.34%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 297 (0.67%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 297 (1.68%)	7 / 295 (2.37%)	
occurrences causally related to treatment / all	2 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 297 (0.34%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 2	
Respiratory tract infection viral			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 297 (1.01%)	4 / 295 (1.36%)	
occurrences causally related to treatment / all	0 / 4	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 297 (0.00%)	2 / 295 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 297 (1.35%)	3 / 295 (1.02%)	
occurrences causally related to treatment / all	2 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 297 (0.34%)	0 / 295 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	0 / 297 (0.00%)	1 / 295 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A - CAP/BEV	Arm B - CAP/BEV/VIN	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	292 / 297 (98.32%)	291 / 295 (98.64%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	85 / 297 (28.62%)	66 / 295 (22.37%)	
occurrences (all)	112	83	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	89 / 297 (29.97%)	125 / 295 (42.37%)	
occurrences (all)	102	155	
General physical health deterioration			
subjects affected / exposed	17 / 297 (5.72%)	19 / 295 (6.44%)	
occurrences (all)	17	22	
Mucosal inflammation			
subjects affected / exposed	57 / 297 (19.19%)	67 / 295 (22.71%)	
occurrences (all)	73	88	
Oedema peripheral			
subjects affected / exposed	16 / 297 (5.39%)	15 / 295 (5.08%)	
occurrences (all)	17	16	
Pain			
subjects affected / exposed	24 / 297 (8.08%)	32 / 295 (10.85%)	
occurrences (all)	26	36	
Pyrexia			

subjects affected / exposed	13 / 297 (4.38%)	28 / 295 (9.49%)	
occurrences (all)	14	38	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	30 / 297 (10.10%)	27 / 295 (9.15%)	
occurrences (all)	32	28	
Dysphonia			
subjects affected / exposed	11 / 297 (3.70%)	18 / 295 (6.10%)	
occurrences (all)	12	20	
Dyspnoea			
subjects affected / exposed	34 / 297 (11.45%)	43 / 295 (14.58%)	
occurrences (all)	35	49	
Epistaxis			
subjects affected / exposed	34 / 297 (11.45%)	59 / 295 (20.00%)	
occurrences (all)	39	68	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	19 / 297 (6.40%)	23 / 295 (7.80%)	
occurrences (all)	20	23	
Investigations			
Weight decreased			
subjects affected / exposed	23 / 297 (7.74%)	36 / 295 (12.20%)	
occurrences (all)	23	37	
Nervous system disorders			
Dizziness			
subjects affected / exposed	21 / 297 (7.07%)	27 / 295 (9.15%)	
occurrences (all)	25	35	
Dysgeusia			
subjects affected / exposed	28 / 297 (9.43%)	26 / 295 (8.81%)	
occurrences (all)	28	28	
Headache			
subjects affected / exposed	41 / 297 (13.80%)	49 / 295 (16.61%)	
occurrences (all)	48	63	
Paraesthesia			
subjects affected / exposed	18 / 297 (6.06%)	17 / 295 (5.76%)	
occurrences (all)	22	21	

Polyneuropathy			
subjects affected / exposed	22 / 297 (7.41%)	45 / 295 (15.25%)	
occurrences (all)	24	48	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 297 (4.04%)	45 / 295 (15.25%)	
occurrences (all)	16	58	
Leukopenia			
subjects affected / exposed	8 / 297 (2.69%)	83 / 295 (28.14%)	
occurrences (all)	9	171	
Neutropenia			
subjects affected / exposed	10 / 297 (3.37%)	80 / 295 (27.12%)	
occurrences (all)	13	155	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	7 / 297 (2.36%)	15 / 295 (5.08%)	
occurrences (all)	7	16	
Abdominal pain upper			
subjects affected / exposed	26 / 297 (8.75%)	43 / 295 (14.58%)	
occurrences (all)	31	53	
Constipation			
subjects affected / exposed	43 / 297 (14.48%)	67 / 295 (22.71%)	
occurrences (all)	52	82	
Diarrhoea			
subjects affected / exposed	92 / 297 (30.98%)	83 / 295 (28.14%)	
occurrences (all)	140	117	
Dyspepsia			
subjects affected / exposed	16 / 297 (5.39%)	26 / 295 (8.81%)	
occurrences (all)	17	27	
Nausea			
subjects affected / exposed	96 / 297 (32.32%)	129 / 295 (43.73%)	
occurrences (all)	119	179	
Stomatitis			
subjects affected / exposed	22 / 297 (7.41%)	25 / 295 (8.47%)	
occurrences (all)	24	35	
Vomiting			

subjects affected / exposed	39 / 297 (13.13%)	51 / 295 (17.29%)	
occurrences (all)	50	64	
Abdominal pain			
subjects affected / exposed	16 / 297 (5.39%)	14 / 295 (4.75%)	
occurrences (all)	20	18	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	20 / 297 (6.73%)	59 / 295 (20.00%)	
occurrences (all)	22	61	
Erythema			
subjects affected / exposed	18 / 297 (6.06%)	8 / 295 (2.71%)	
occurrences (all)	18	9	
Nail disorder			
subjects affected / exposed	17 / 297 (5.72%)	11 / 295 (3.73%)	
occurrences (all)	17	12	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	195 / 297 (65.66%)	119 / 295 (40.34%)	
occurrences (all)	305	174	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	23 / 297 (7.74%)	19 / 295 (6.44%)	
occurrences (all)	38	28	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 297 (7.41%)	29 / 295 (9.83%)	
occurrences (all)	24	30	
Back pain			
subjects affected / exposed	20 / 297 (6.73%)	28 / 295 (9.49%)	
occurrences (all)	21	29	
Bone pain			
subjects affected / exposed	26 / 297 (8.75%)	24 / 295 (8.14%)	
occurrences (all)	28	27	
Muscle spasms			
subjects affected / exposed	7 / 297 (2.36%)	16 / 295 (5.42%)	
occurrences (all)	7	19	
Pain in extremity			

subjects affected / exposed	20 / 297 (6.73%)	26 / 295 (8.81%)	
occurrences (all)	22	29	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	27 / 297 (9.09%)	32 / 295 (10.85%)	
occurrences (all)	32	47	
Urinary tract infection			
subjects affected / exposed	28 / 297 (9.43%)	29 / 295 (9.83%)	
occurrences (all)	35	33	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	39 / 297 (13.13%)	45 / 295 (15.25%)	
occurrences (all)	41	57	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 June 2009	A first revision of the initial study protocol introduced the project "Translational research"
23 September 2009	The substantial amendment 1 introduced the project "Epigenetic Profiling of Plasma DNA in Response to Chemotherapy Treatment"
14 March 2011	The substantial amendment 2 included the capture of laboratory values extended even to laboratory values considered non-pathological, and the capture of tumor evaluations independent of individual treatment cycles.
09 August 2011	The substantial amendment 3 included the increase of the patient number from initial 400 to 600, and the changeover of capecitabine and bevacizumab to articles of trade.
21 October 2014	The substantial amendment 4 issued the classification of the trial. The trial phase was changed from IIb to phase III. Further, the number of events for the primary endpoint analysis was reduced due to the unexpected high drop-out rate. The original sample size calculation assumed 494 events, the amended sample size included at least 441 events, yielding 75% power to detect a PFS difference between treatment arms.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported