Clinical trial results:
A randomized phase III study of standard treatment +/- enoxaparin in small cell lung cancer.

Summary

EudraCT number	2007-006033-14
Trial protocol	SE DK
Global end of trial date	05 May 2017

Results information

Result version number	v1 (current)
This version publication date	22 July 2021
First version publication date	22 July 2021
Summary attachment (see zip file)	Publication. Annals of Oncology (RASTEN.Annals of Oncology.pdf)

Trial information

Trial identification

Sponsor protocol code	Version 10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00717938
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Lund University Hospital
Sponsor organisation address	Getingevägen 4, Lund, Sweden, 221 85
Public contact	Jan Sundberg, Lund University Hospital, +46 46 17 70 34, jan.sundberg@skane.se
Scientific contact	Lars Ek, Lund University Hospital, +46 46 17 10 00, l.ek@icloud.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	05 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 May 2017
Global end of trial reached?	Yes
Global end of trial date	05 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective with the study was to evaluate treatment with chemotherapy with a platinum- and a topoisomeras inhibitor containing regimen versus treatment with the same chemotherapy with addition of low molecular weight heparin, in this case enoxaparin, comparing overall survival.

Protection of trial subjects:

The study treatment (enoxaparin) was stopped permanently if one of the following occured:

- In case of major bleeding, defined as a decrease in Hemoglobin > 20g/L or that leads to transfusion of two or more units of red blood cells.
- Any bleeding intracranially.
- If the patient developed deep venous thrombosis, pulmonary embolism or any other absolute indication for anticoagulant therapy such as LMWH or warfarine.
- If a persistant decrease in platelets (< 50 x10 9/L) is observed and can not be explained by the chemotherapy, HIT (heparin induced thrombocytopenia) must be considered.
- Any other reason at investigators discretion.
- All patients undergone physical examination every third week.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	02 April 2008
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	Sweden: 345
Country: Number of subjects enrolled	Denmark: 13
Country: Number of subjects enrolled	Canada: 32
Worldwide total number of subjects	390
EEA total number of subjects	358

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)	152
From 65 to 84 years	236
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Patients with newly diagnosed small cell lung cancer, suitable for chemotherapy treatment containing cisplatinum and a topoisemerasinhibitor for 4-6 cycles were screened for inclusion in the trial. Included patients were randomised between standard treatment (control arm, arm A) or chemotherapy with addition of enoxaparin, experimental arm.

Pre-assignment

Screening details:

Patients were screened for normal coagulation status, before entering the trial.

Pre-assignment period milestones

Number of subjects started	390
Number of subjects completed	390

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 (control arm)

Arm description:

Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm.

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

Dosage and administration details:

Was given every third week at a dose of 75 mg/m2.

Investigational medicinal product name	Karboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of AUC 5.

Investigational medicinal product name	Irinotekan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of 175 mg/m2.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of 100 mg/m2.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Was given every third week at a dose of 100 mg/m2.

Investigational medicinal product name	Topotekan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of 1.5 mg/m2.

Arm title	Arm B (experimental arm)

Arm description:

Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm, plus the addition of enoxaparine, 1 mg/kilogram bodyweigt, given daily subcutaneously during chemotherapy treatment.

Arm type	Experimental
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of 75 mg/m2.

Investigational medicinal product name	Karboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of AUC 5.

Investigational medicinal product name	Irinotekan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Was given every third week at a dose of 175 mg/m2.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use
Dosage and administration details: Was given every third week at a dose of 100 mg/m2.	
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Was given every third week at a dose of 100 mg/m2.	
Investigational medicinal product name	Topotekan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Was given every third week at a dose of 1.5 mg/m2.	
Investigational medicinal product name	Klexane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Was given in thde experimental arm once daily during chemotherpt, at a dose of 1 mg/kg bodyweight.	

Number of subjects in period 1	Arm A (control arm)	Arm B (experimental arm)
Started	195	195
Completed	195	195

Baseline characteristics

Reporting groups

Reporting group title	Arm A (control arm)

Reporting group description:

Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm.

Reporting group title	Arm B (experimental arm)

Reporting group description:

Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm, plus the addition of enoxaparine, 1 mg/kilogram bodyweigt, given daily subcutaneously during chemotherapy treatment.

Reporting group values	Arm A (control arm)	Arm B (experimental arm)	Total
Number of subjects	195	195	390
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)	73	75	148
From 65-84 years	121	120	241
85 years and over	1	0	1
Age continuous Units: years			
median	68	68	
full range (min-max)	62 to 73	62 to 73	-
Gender categorical Units: Subjects			
Female	115	113	228
Male	80	82	162

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Per protocol

Subject analysis set description:

Overall survival was evaluated at time from randomisation to death of any cause.

Reporting group values	Overall trial		
Number of subjects	390		
Age categorical Units: Subjects			
In utero	0		

Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	148		
From 65-84 years	241		
85 years and over	1		
Age continuous			
Units: years			
median	68		
full range (min-max)	62 to 73		
Gender categorical			
Units: Subjects			
Female	228		
Male	162		

End points

End points reporting groups

Reporting group title	Arm A (control arm)
Reporting group description:	
Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm.	
Reporting group title	Arm B (experimental arm)
Reporting group description:	
Standard chemotherapy including platinum- and a topoisomerase inhibitor for 4-6 cycles (cycle length 21 days), investigators choice, control arm, plus the addition of enoxaparine, 1 mg/kilogram bodyweigt, given daily subcutaneously during chemotherapy treatment.	
Subject analysis set title	Overall trial
Subject analysis set type	Per protocol
Subject analysis set description:	
Overall survival was evaluated at time from randomisation to death of any cause.	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
Survival duration is measured from the date of randomization to the date of death from any cause.	

End point values	Arm A (control arm)	Arm B (experimental arm)	Overall trial	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	195	195	390	
Units: Months				
number (confidence interval 0.75%)	195 (190 to 200)	195 (190 to 200)	390 (380 to 400)	

Statistical analyses

Statistical analysis title	Survival analysis
Comparison groups	Arm A (control arm) v Arm B (experimental arm)
Number of subjects included in analysis	390
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the day the patient was randomized in the trial until 30 days after last treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	163 / 390 (41.79%)		
number of deaths (all causes)	28		
number of deaths resulting from adverse events	0		
Vascular disorders			
Bleeding			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 2		
Brain infarction			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac infarction			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombosis			

subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Detoriation general condition			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 2		
Fatigue			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	6 / 390 (1.54%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Pleural infection			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive lung disease			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pleural effusion				
subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	5 / 390 (1.28%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 2			
Respiratory failure				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	0 / 377			
deaths causally related to treatment / all	0 / 0			
Investigations				
Increased creatinine				
subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Glucose increased				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcemia				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypocalcemia				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Hypomagnesemia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatremia			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrhythmia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			

subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Neuropathy				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anemia				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	16 / 390 (4.10%)			
occurrences causally related to treatment / all	2 / 16			
deaths causally related to treatment / all	2 / 2			
Hematemesis				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelodysplastic syndrome unclassifiable				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Neutropenia				

subjects affected / exposed	8 / 390 (2.05%)			
occurrences causally related to treatment / all	1 / 8			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	4 / 390 (1.03%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colon perforation				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Diarrhéa				
subjects affected / exposed	10 / 390 (2.56%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 0			
Esophagitis				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	8 / 390 (2.05%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Urinary retention				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	3 / 390 (0.77%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Muscle weakness				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infection				
subjects affected / exposed	45 / 390 (11.54%)			
occurrences causally related to treatment / all	0 / 45			
deaths causally related to treatment / all	0 / 9			
Cystitis				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Herpesencephalitis				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Septic infection				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	1 / 1			
Pneumonia				
subjects affected / exposed	4 / 390 (1.03%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			

Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 390 (27.95%)		
Vascular disorders			
Bleeding			
subjects affected / exposed	4 / 390 (1.03%)		
occurrences (all)	4		
Pulmonary embolus			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Thrombosis			
subjects affected / exposed	10 / 390 (2.56%)		
occurrences (all)	10		
Haematoma			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 390 (1.03%)		
occurrences (all)	4		
Chills			

subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	5 / 390 (1.28%)		
occurrences (all)	5		
Fever			
subjects affected / exposed	8 / 390 (2.05%)		
occurrences (all)	8		
Immune system disorders			
Allergy			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pulmonary bleeding			
subjects affected / exposed	11 / 390 (2.82%)		
occurrences (all)	11		
Bronkitis			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Coagh			
subjects affected / exposed	7 / 390 (1.79%)		
occurrences (all)	7		
Dyspnea			
subjects affected / exposed	16 / 390 (4.10%)		
occurrences (all)	16		
Pulmonary emphysema			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	9 / 390 (2.31%)		
occurrences (all)	9		
Haemoptysis			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Hypoxia			

subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Pulmonary infiltrates			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Voice changes			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 390 (1.28%)		
occurrences (all)	5		
Depression			
subjects affected / exposed	6 / 390 (1.54%)		
occurrences (all)	6		
Hallucinations			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		
Somnolence			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Investigations			
Creatinine increased			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		
Blood glucose increased			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Hypercalcemia			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Hypocalcemia			

subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Hypokalemia			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		
Hypomagnesemia			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		
Hyponatremia			
subjects affected / exposed	10 / 390 (2.56%)		
occurrences (all)	10		
Increased ALAT			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Weight loss			
subjects affected / exposed	7 / 390 (1.79%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Dental injury			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Atrial fibrillation			
subjects affected / exposed	4 / 390 (1.03%)		
occurrences (all)	4		
Cardiac arrest			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Cardiac arrythmia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Cardiac failure			

subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Cardiac infarction			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Neuropathia			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	9 / 390 (2.31%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	15 / 390 (3.85%)		
occurrences (all)	15		
Restless legs			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Seizure			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Speech impairment			
subjects affected / exposed	2 / 390 (0.51%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Transitorisk ischemisk attack			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		

Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	21 / 390 (5.38%)		
occurrences (all)	21		
Thrombocytopenia			
subjects affected / exposed	13 / 390 (3.33%)		
occurrences (all)	13		
Ear and labyrinth disorders			
Decreased hearing			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Dry eyes			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Iritis			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 390 (1.28%)		
occurrences (all)	5		
Bleeding from ulcus ventriculi			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Rectal bleeding			
subjects affected / exposed	3 / 390 (0.77%)		
occurrences (all)	3		

Colon rupture				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			
Constipation				
subjects affected / exposed	10 / 390 (2.56%)			
occurrences (all)	10			
Diarréa				
subjects affected / exposed	20 / 390 (5.13%)			
occurrences (all)	20			
Dysphagia				
subjects affected / exposed	10 / 390 (2.56%)			
occurrences (all)	10			
Eosophagitis				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			
Epigastralgia				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			
Esophagitis				
subjects affected / exposed	8 / 390 (2.05%)			
occurrences (all)	8			
Flatulence				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			
Fracture				
subjects affected / exposed	5 / 390 (1.28%)			
occurrences (all)	5			
Gastritis				
subjects affected / exposed	2 / 390 (0.51%)			
occurrences (all)	2			
Gastroenteritis				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			
Gastrointestinal bleeding				
subjects affected / exposed	1 / 390 (0.26%)			
occurrences (all)	1			

Vomiting subjects affected / exposed occurrences (all)	10 / 390 (2.56%) 10		
Stomatitis subjects affected / exposed occurrences (all)	2 / 390 (0.51%) 2		
Taste alteration subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Skin and subcutaneous tissue disorders			
Bruising subjects affected / exposed occurrences (all)	2 / 390 (0.51%) 2		
Dry skin subjects affected / exposed occurrences (all)	2 / 390 (0.51%) 2		
Ecchymosis subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Pruritus subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Rash subjects affected / exposed occurrences (all)	6 / 390 (1.54%) 6		
Urticaria subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Renal and urinary disorders			
Urinary urgency subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain subjects affected / exposed occurrences (all)	19 / 390 (4.87%) 19		

Back pain			
subjects affected / exposed	7 / 390 (1.79%)		
occurrences (all)	7		
Cramps			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Hallux valgus			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Infections and infestations			
Infection			
subjects affected / exposed	13 / 390 (3.33%)		
occurrences (all)	13		
Caliciinfection			
subjects affected / exposed	4 / 390 (1.03%)		
occurrences (all)	4		
Cystitis			
subjects affected / exposed	6 / 390 (1.54%)		
occurrences (all)	6		
Epydidemitis			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 390 (0.26%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	8 / 390 (2.05%)		
occurrences (all)	8		
Viral syndrome			

subjects affected / exposed occurrences (all)	1 / 390 (0.26%) 1		
Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all)	 1 / 390 (0.26%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2009	Addition of a substudy, in which analysis of circulating tumour cells in peripheral blood was performed. Participation in this substudy was not mandatory for the patient. A special written informed concent form was signed by the patient if he/she was willing to participate. Addition of a new site.
15 October 2012	Extended risk-benefit description

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29106448