Clinical trial results:
A randomised phase II/III study of Docetaxel plus Prednisolone vs. Docetaxel plus Prednisolone plus Zoledronic acid vs. Docetaxel plus Prednisolone plus Strontium-89 vs. Docetaxel plus Prednisolone plus Zoledronic Acid plus Strontium-89 in Hormone Refractory Prostate Cancer metastatic to bone.

Summary

EudraCT number	2004-002295-41
Trial protocol	GB
Global end of trial date	01 March 2016

Results information

Result version number	v1 (current)
This version publication date	29 March 2017
First version publication date	29 March 2017

Trial information

Trial identification

Sponsor protocol code	PR2100

Additional study identifiers

ISRCTN number	ISRCTN12808747
ClinicalTrials.gov id (NCT number)	NCT00554918
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	TRAPEZE Trial Office Cancer Research Clinical Trials Unit University of Birmingham, TRAPEZE Trial Office Cancer Research Clinical Trials Unit University of Birmingham, Trapeze@trials.bham.ac.uk
Scientific contact	TRAPEZE Trial Office Cancer Research Clinical Trials Unit University of Birmingham, TRAPEZE Trial Office Cancer Research Clinical Trials Unit University of Birmingham, Trapeze@trials.bham.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 September 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 August 2013
Global end of trial reached?	Yes
Global end of trial date	01 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The Phase II study, concerned the feasiblity, tolerablity and safety in terms of combining docetaxel with zoledronic acid and strontium-89; the phase II data was incorporated into the phase III data for analysis.

The Phase III primary endpoints were :
- Clinical Progression-free survival
- Cost and cost effectiveness of trial treatments

All data including graphs were published with open access in 2016. Please refer to the publications listed in Online Reference section of this report for further and more detailed trial results.

Protection of trial subjects:

This study was carried out in accordance with the World Medical Association (WMA) Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments.
The protocol gained ethical approval from the South West MREC. Before entering patients into the study, the Principal Investigator ensured that the protocol had approval from their local Research Ethics Committee and local Research and Development (R&D) Office.

A participant's tolerance to trial treatment and the overall tumour response was determined by the treating physician who decided whether it was in the participant's best interest to continue with treatment or not. Participants were provided with ethically approved comprehensive information about the trial and trial treatments, and given advice on who to contact with any questions or concerns at any time.

Prophylactic anti-emetic treatment(s) were advised throughout chemotherapy. Dexamethasone and a second anti-emetic, such as metoclopramide, or local standard treatment were recommended. More aggressive anti-emetic treatment, e.g. 5-HT3 antagonists, was advised for participants who experienced CTC AE (i.e. Common Terminology Criteria for Adverse Events, version 3) grade 3 or higher nausea/vomiting in a preceding cycle. If grade 3 or higher symptoms continued, the docetaxel dose was to be reduced by one dose level (i.e. standard dose 75 mg/square meters down to 60 mg/sq. meters, or 60 mg/sq. meters down to 45 mg/sq. meters). Participants with continuing grade 3 or higher nausea/vomiting were withdrawn from trial treatment. Only one docetaxel dose reduction was permitted.

Expected adverse reactions to docetaxel, zoledronic acid (ZA) and Strontium-89 (Sr-89) were itemised in the protocol with guidance and recommended counter measures.

Background therapy:

All supportive care medications, including:
- Prednisolone - Although listed as an investigational medicinal product (IMP) this was essential NICE-recommended supportive care throughout chemotherapy regimens;
- Anti-emetic medications;
- Vitamin D and calcium supplements throughout ZA treatment. For participants also treated with Sr89, vitamin D/calcium supplements were halted 3 weeks prior to and recommenced 4 weeks after SR89 administration.

Evidence for comparator:

Docetaxel therapy plus prednisolone for up to 10 cycles/3-weekly became the mainstay of standard therapy for metastatic, castrate (previously 'hormone') refractory prostate cancer (CRPC, previously referred to as HRPC) – approved by the National Institute for Health and Clinical Excellence (NICE) in 2006, following two landmark trials published in the New England Journal of Medicine in 2004 (Tannock et al. 2004; Petrylak et al, 2004).

One of the commonest sites of spread, and major cause of morbidity, in metastatic CRPC is to bone. ZA and Sr89 are two of the treatments approved for the treatment of bone disease. A pre-docetaxel era trial combined chemotherapy with Sr89 in a small randomized trial and suggested a survival advantage in patients allocated to Sr89 (Tu et al, 2001). Zoledronic acid was approved on the basis of reductions in skeletal related events (SREs) demonstrated in randomised studies in mHRPC (Saad et al, 2004).

Tannock IF, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-12. Epub 2004/10/08.

Petrylak DP, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. NEnglJ Med. 2004;351(15):1513-20.

Tu SM, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial.[erratum appears in Lancet 2001 Apr 14;357(9263):1210]. Lancet. 2001;357(9253):336-41.

Saad F, et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. J NatlCancer Inst. 2004;96(11):879-82.

Actual start date of recruitment	04 February 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 757
Worldwide total number of subjects	757
EEA total number of subjects	757

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)	194
From 65 to 84 years	563
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited between 04-Feb-2005 and 29-Feb-2012 at multiple centres in the United Kingdom.

Pre-assignment

Screening details:

Eligible participants were male, ≥18yrs, ≥1 bone mets, ECOG 1-2 with adequate haema/renal/hepatic function
Exclusions : prior chemotherapy or radionuclide therapy for CRPC, prior radiotherapy to >25% bone marrow, bisphosphonate therapy within 2 months of trial entry, other malignant disease in last 5yrs, brain mets, peripheral neuropathy

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Control – Docetaxel plus prednisolone (Standard care)
Pre-treatment period

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment period.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pre-treatment period.

Arm title	Arm B

Arm description:

Docetaxel plus prednisolone plus zoledronic acid
Pre-treatment period

Arm type	Experimental

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment period.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pre-treatment period

Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	PR2
Other name	Zometa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment period.

Arm title	Arm C

Arm description:

Docetaxel plus prednisolone plus Strontium-89 (Sr89)
Pre-treatment period

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment period.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Pre-treatment period.

Investigational medicinal product name	Strontium (89Sr) chloride
Investigational medicinal product code	PR3
Other name	Metastron, Sr89
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

Pre-treatment period.

Arm title	Arm D

Arm description:

Docetaxel plus prednisolone plus ZA plus Sr89
Pre-treatment period

Arm type	Experimental

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Pre-treatment period.	
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Pre-treatment period.	
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	PR2
Other name	Zometa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Pre-treatment period.	
Investigational medicinal product name	Strontium (89Sr) chloride
Investigational medicinal product code	PR3
Other name	Metastron, Sr89
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use
Dosage and administration details: Pre-treatment period.	

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	191	188	190
Allocation	191	188	190
Completed	191	188	190

Number of subjects in period 1	Arm D
Started	188
Allocation	188
Completed	188

Period 2

Period 2 title	Treatment and Follow Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Control – Docetaxel plus prednisolone (Standard care)
No further docetaxel or prednisolone treatment was administered during the follow-up stage.

Arm type	Active comparator
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Post-treatment period.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Post-treatment period.

Arm title	Arm B

Arm description:

During the follow-up period 4-weekly ZA continued as clinical indicated, until disease progression or other discontinuation criteria.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	PR2
Other name	Zometa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg i.v. every 4 weeks starting one month after final chemotherapy cycle, as clinically indicated or until disease-progression or other discontinuation criteria.

Patients treated with zoledronic acid also received vitamin D and calcium supplements throughout treatment.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As per Arm A

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per Arm A

Arm title	Arm C

Arm description:

No further chemotherapy, prednisolone or Sr89 was offered during the follow-up period.

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As per Arm A; Cycle 7 Docetaxel given between 28 and 56 days post-Sr89 administration subject to satisfactory pre-chemotherapy assessment.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per Arm A

Investigational medicinal product name	Strontium (89Sr) chloride
Investigational medicinal product code	PR3
Other name	Metastron, Sr89
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

Sr89 150 MBq i.v. once, 28 days after the 6th cycle of docetaxel therapy subject to acceptable pre-administration assessment.

Arm title	Arm D

Arm description:

As per Arm B, ZA continued on a monthly (4-weekly) basis during the follow-up period as clinically indicated, until protocol defined disease progression or othr discontinuation criteria. No further chemotherapy, prednisolone or Sr89 were given during the follow-up period.

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	PR2
Other name	Zometa
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

4 mg i.v. every 4 weeks starting one month after final chemotherapy cycle, as clinically indicated or until disease-progression or other discontinuation criteria.

Patients treated with zoledronic acid also received vitamin D and calcium supplements throughout treatment.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	PR1
Other name	Taxotere
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

As per Arm A; Cycle 7 Docetaxel given between 28 and 56 days post-Sr89 administration subject to satisfactory pre-chemotherapy assessment.

Investigational medicinal product name	Prednisolone
Investigational medicinal product code	PR4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per Arm A

Investigational medicinal product name	Strontium (89Sr) chloride
Investigational medicinal product code	PR3
Other name	Metastron, Sr89
Pharmaceutical forms	Sterile concentrate
Routes of administration	Intravenous use

Dosage and administration details:

As per Arm C

Number of subjects in period 2	Arm A	Arm B	Arm C
Started	191	188	190
Completed	188	188	189
Not completed	3	0	1
Lost to follow-up	3	-	1

Number of subjects in period 2	Arm D
Started	188
Completed	186
Not completed	2
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Control – Docetaxel plus prednisolone (Standard care) Pre-treatment period	

Reporting group title	Arm B
Reporting group description:	
Docetaxel plus prednisolone plus zoledronic acid Pre-treatment period	
Reporting group title	Arm C
Reporting group description:	
Docetaxel plus prednisolone plus Strontium-89 (Sr89) Pre-treatment period	
Reporting group title	Arm D
Reporting group description:	
Docetaxel plus prednisolone plus ZA plus Sr89 Pre-treatment period	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	191	188	190
Age categorical Units: Subjects			
Adults from 18-84 years	191	188	190
Age continuous			
Age at randomisation			
Units: years			
median	68.7	69.4	68.3
inter-quartile range (Q1-Q3)	64.3 to 73.8	64.4 to 73.7	62.9 to 72.9
Gender categorical			
All trial participants were male.			
Units: Subjects			
Female	0	0	0
Male	191	188	190
ECOG performance status Units: Subjects			
Score 0	76	71	70
Score 1	83	88	90
Score 2	15	15	18
Score 3	1	0	0
Not recorded	16	14	12
Diagnostic indicator			
Method by which prostate cancer was diagnosed.			
Units: Subjects			
Adenocarcinoma	156	146	150
PSA only	35	39	37
Missing	0	3	3
Staging : T			

Staging information : T value			
Units: Subjects			
T1	2	5	2
T1b	1	0	1
T1c	0	1	2
T2	19	16	11
T2a	2	2	0
T2b	4	1	1
T3	54	53	49
T3a	4	3	5
T3b	12	10	10
T4	28	22	20
TX	16	18	20
T2c	1	0	0
Missing	48	57	69
Staging : M			
Staging scores : M values			
Units: Subjects			
M0	44	41	33
M1a	20	20	22
M1b	8	7	3
M1c	4	10	6
MX	26	14	17
M1	41	39	40
Missing	48	57	69
Staging : N			
Staging : N values			
Units: Subjects			
N0	59	57	46
N1	42	28	32
NX	42	46	43
Missing	48	57	69
Gleason score Units: Subjects			
03	0	0	0
04	2	0	1
05	2	3	2
06	9	12	12
07	43	48	39
08	30	24	35
09	57	55	41
10	1	1	8
Missing	47	45	52
Prior radiotherapy received			
Number of participants who received radiotherapy prior to randomisation			
Units: Subjects			
No	114	107	95
Yes	77	80	92
Missing	0	1	3
Method of castration Units: Subjects			

Surgery	5	4	3
Ongoing LHRH agonists	186	184	187
Participants receiving anti-androgen Units: Subjects			
No	10	19	17
Yes	181	168	170
Missing	0	1	3
Participants receiving flutamide, nilutamide or cyprooterone acetate Units: Subjects			
Not received	151	141	142
Received	29	27	27
Missing	11	20	21
Participants who received bicalutamide Units: Subjects			
Not received	11	14	8
Received	170	154	162
Missing	10	20	20
Method used to determine progression at trial entry Units: Subjects			
All methods	26	27	27
Elevated PSA	42	48	42
New lesion	15	16	21
Objective	5	1	1
Objective + new lesion	3	4	7
PSA + new lesion	94	85	82
PSA + objective	5	4	8
Missing	1	3	2

Reporting group values	Arm D	Total	
Number of subjects	188	757	
Age categorical Units: Subjects			
Adults from 18-84 years	188	757	
Age continuous			
Age at randomisation			
Units: years			
median	68.9		
inter-quartile range (Q1-Q3)	64 to 73.1	-	
Gender categorical			
All trial participants were male.			
Units: Subjects			
Female	0	0	
Male	188	757	
ECOG performance status Units: Subjects			
Score 0	64	281	
Score 1	95	356	
Score 2	14	62	
Score 3	0	1	
Not recorded	15	57	

Diagnostic indicator			
Method by which prostate cancer was diagnosed.			
Units: Subjects			
Adenocarcinoma	149	601	
PSA only	35	146	
Missing	4	10	
Staging : T			
Staging information : T value			
Units: Subjects			
T1	1	10	
T1b	0	2	
T1c	1	4	
T2	17	63	
T2a	0	4	
T2b	2	8	
T3	63	219	
T3a	4	16	
T3b	9	41	
T4	25	95	
TX	18	72	
T2c	1	2	
Missing	47	221	
Staging : M			
Staging scores : M values			
Units: Subjects			
M0	40	158	
M1a	21	83	
M1b	2	20	
M1c	5	25	
MX	26	83	
M1	47	167	
Missing	47	221	
Staging : N			
Staging : N values			
Units: Subjects			
N0	58	220	
N1	39	141	
NX	44	175	
Missing	47	221	
Gleason score Units: Subjects			
03	1	1	
04	0	3	
05	3	10	
06	6	39	
07	41	171	
08	25	114	
09	54	207	
10	4	14	
Missing	54	198	
Prior radiotherapy received			

Number of participants who received radiotherapy prior to randomisation			
Units: Subjects			
No	98	414	
Yes	88	337	
Missing	2	6	
Method of castration Units: Subjects			
Surgery	2	14	
Ongoing LHRH agonists	186	743	
Participants receiving anti-androgen Units: Subjects			
No	14	60	
Yes	171	690	
Missing	3	7	
Participants receiving flutamide, nilutamide or cyprooterone acetate Units: Subjects			
Not received	133	567	
Received	38	121	
Missing	17	69	
Participants who received bicalutamide Units: Subjects			
Not received	15	48	
Received	156	642	
Missing	17	67	
Method used to determine progression at trial entry Units: Subjects			
All methods	27	107	
Elevated PSA	44	176	
New lesion	19	71	
Objective	1	8	
Objective + new lesion	5	19	
PSA + new lesion	88	349	
PSA + objective	2	19	
Missing	2	8	

Subject analysis sets

Subject analysis set title	ZA
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Factorial analysis 1 : ZA with no ZA, stratified by Sr89.
Thus, Arms B and D (ZA) were compared with arms A and C (No ZA)

Subject analysis set title	Sr89
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Factorial analsyis 2 : Sr89 with no Sr89, stratified by ZA.
Thus, Arms C and D (Sr89) were compared with arms A and B (No Sr89).

Subject analysis set title	No ZA
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Factorial analysis 1 : ZA with no ZA, stratified by Sr89.
Thus, Arms A and C (No ZA)were compared with Arms B and D (ZA)

Subject analysis set title	No Sr89
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Factorial analsyis 2 : Sr89 with no Sr89, stratified by ZA.
Thus, Arms A and B (No Sr89) were compared with Arms C and D (Sr89).

Reporting group values	ZA	Sr89	No ZA
Number of subjects	376	378	381
Age categorical Units: Subjects			
Adults from 18-84 years	376	378	
Age continuous			
Age at randomisation			
Units: years			
median	68.9	68.6	68.6
inter-quartile range (Q1-Q3)	64.1 to 73.4	63.2 to 73.1	63.6 to 73.5
Gender categorical			
All trial participants were male.			
Units: Subjects			
Female	0	0	0
Male	376	378	381
ECOG performance status Units: Subjects			
Score 0	135	134	146
Score 1	183	185	173
Score 2	29	32	33
Score 3	0	0	1
Not recorded	26	23	26
Diagnostic indicator			
Method by which prostate cancer was diagnosed.			
Units: Subjects			
Adenocarcinoma	295	299	306
PSA only	74	72	72
Missing	4	3	1
Staging : T			
Staging information : T value			
Units: Subjects			
T1	6	3	4
T1b	0	1	2
T1c	2	3	2
T2	33	28	30
T2a	2	0	2
T2b	3	3	5
T3	116	112	103
T3a	7	9	9
T3b	19	19	22
T4	47	45	48
TX	36	38	36
T2c	1	1	1

Missing	101	112	115
Staging : M			
Staging scores : M values			
Units: Subjects			
M0	81	73	77
M1a	41	43	42
M1b	9	5	11
M1c	15	11	10
MX	40	43	43
M1	86	87	81
Missing	101	112	115
Staging : N			
Staging : N values			
Units: Subjects			
N0	115	104	105
N1	67	71	74
NX	90	87	85
Missing	101	112	115
Gleason score Units: Subjects			
03	1	1	0
04	0	1	3
05	6	5	4
06	18	18	21
07	89	80	82
08	49	60	65
09	109	95	98
10	5	12	9
Missing	96	102	97
Prior radiotherapy received			
Number of participants who received radiotherapy prior to randomisation			
Units: Subjects			
No	205	193	209
Yes	168	180	169
Missing	0	1	1
Method of castration Units: Subjects			
Surgery	6	5	8
Ongoing LHRH agonists	367	369	371
Participants receiving anti-androgen Units: Subjects			
No	33	31	27
Yes	339	341	351
Missing	0	2	0
Participants receiving flutamide, nilutamide or cyprooterone acetate Units: Subjects			
Not received	274	275	293
Received	65	65	56
Missing	37	38	32
Participants who received bicalutamide			

Units: Subjects			
Not received	29	23	19
Received	310	318	332
Missing	34	33	28
Method used to determine progression at trial entry Units: Subjects			
All methods	54	54	53
Elevated PSA	92	86	84
New lesion	35	40	36
Objective	2	2	6
Objective + new lesion	9	12	10
PSA + new lesion	173	170	176
PSA + objective	6	10	13
Missing	2	0	1

Reporting group values	No Sr89		
Number of subjects	379		
Age categorical Units: Subjects			
Adults from 18-84 years			
Age continuous			
Age at randomisation			
Units: years			
median	68.9		
inter-quartile range (Q1-Q3)	64.3 to 73.8		
Gender categorical			
All trial participants were male.			
Units: Subjects			
Female	0		
Male	379		
ECOG performance status Units: Subjects			
Score 0	147		
Score 1	171		
Score 2	30		
Score 3	1		
Not recorded	29		
Diagnostic indicator			
Method by which prostate cancer was diagnosed.			
Units: Subjects			
Adenocarcinoma	302		
PSA only	74		
Missing	2		
Staging : T			
Staging information : T value			
Units: Subjects			
T1	7		
T1b	1		
T1c	1		
T2	35		

T2a	4		
T2b	5		
T3	107		
T3a	7		
T3b	22		
T4	50		
TX	34		
T2c	1		
Missing	104		
Staging : M			
Staging scores : M values			
Units: Subjects			
M0	85		
M1a	40		
M1b	15		
M1c	14		
MX	40		
M1	80		
Missing	104		
Staging : N			
Staging : N values			
Units: Subjects			
N0	116		
N1	70		
NX	88		
Missing	104		
Gleason score Units: Subjects			
03	0		
04	2		
05	5		
06	21		
07	91		
08	54		
09	112		
10	2		
Missing	91		
Prior radiotherapy received			
Number of participants who received radiotherapy prior to randomisation			
Units: Subjects			
No	221		
Yes	157		
Missing	0		
Method of castration Units: Subjects			
Surgery	9		
Ongoing LHRH agonists	369		
Participants receiving anti-androgen Units: Subjects			
No	29		
Yes	349		

Missing	0		
Participants receiving flutamide, nilutamide or cyprooterone acetate Units: Subjects			
Not received	292		
Received	56		
Missing	31		
Participants who received bicalutamide Units: Subjects			
Not received	25		
Received	324		
Missing	29		
Method used to determine progression at trial entry Units: Subjects			
All methods	53		
Elevated PSA	90		
New lesion	31		
Objective	6		
Objective + new lesion	7		
PSA + new lesion	179		
PSA + objective	9		
Missing	3		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Control – Docetaxel plus prednisolone (Standard care) Pre-treatment period	

Reporting group title	Arm B
Reporting group description:	
Docetaxel plus prednisolone plus zoledronic acid Pre-treatment period	
Reporting group title	Arm C
Reporting group description:	
Docetaxel plus prednisolone plus Strontium-89 (Sr89) Pre-treatment period	
Reporting group title	Arm D
Reporting group description:	
Docetaxel plus prednisolone plus ZA plus Sr89 Pre-treatment period	
Reporting group title	Arm A
Reporting group description:	
Control – Docetaxel plus prednisolone (Standard care) No further docetaxel or prednisolone treatment was administered during the follow-up stage.	
Reporting group title	Arm B
Reporting group description:	
During the follow-up period 4-weekly ZA continued as clinical indicated, until disease progression or other discontinuation criteria.	
Reporting group title	Arm C
Reporting group description:	
No further chemotherapy, prednisolone or Sr89 was offered during the follow-up period.	
Reporting group title	Arm D
Reporting group description:	
As per Arm B, ZA continued on a monthly (4-weekly) basis during the follow-up period as clinically indicated, until protocol defined disease progression or othr discontinuation criteria. No further chemotherapy, prednisolone or Sr89 were given during the follow-up period.	
Subject analysis set title	ZA
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Factorial analysis 1 : ZA with no ZA, stratified by Sr89. Thus, Arms B and D (ZA) were compared with arms A and C (No ZA)	
Subject analysis set title	Sr89
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Factorial analsyis 2 : Sr89 with no Sr89, stratified by ZA. Thus, Arms C and D (Sr89) were compared with arms A and B (No Sr89).	
Subject analysis set title	No ZA
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Factorial analysis 1 : ZA with no ZA, stratified by Sr89. Thus, Arms A and C (No ZA)were compared with Arms B and D (ZA)	
Subject analysis set title	No Sr89
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Factorial analsyis 2 : Sr89 with no Sr89, stratified by ZA.
Thus, Arms A and B (No Sr89) were compared with Arms C and D (Sr89).

Primary: Clinical Progression-Free Survival (CPFS) - ZA comparison

End point title	Clinical Progression-Free Survival (CPFS) - ZA comparison

End point description:

The primary Phase III analysis compared ZA versus no ZA (stratified for Sr-89 use) and Sr-89 versus no Sr-89 (stratified for ZA use) in terms of CPFS. CPFS was defined as the number of whole days from the date of randomisation to the first occurrence of SRE, pain progression or death. Patients not experiencing clinical progression were censored at the date last known to be progression free.

End point type	Primary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	ZA	No ZA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	381		
Units: Days				
Death	122	87		
Skeletal-related event (SRE)	56	73		
Pain	132	132		
Death SRE	1	0		
SRE pain	41	52		

Statistical analyses

Statistical analysis title	Unadjusted log rank

Statistical analysis description:

The first analysis of the primary outcome was an unadjusted stratified log-rank test comparing ZA with no ZA, stratified by Sr-89.

Comparison groups	ZA v No ZA
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7553 [1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.13

Notes:

[1] - In total, there were 696 events: 352 (51%) in the ZA group and 344 (49%) in the no ZA. A stratified log-rank test was performed comparing ZA and no ZA. No statistical difference in CPFS between the two groups was observed ($\chi 2 = 0.10$; $p = 0.7553$)

Statistical analysis title	Adjusted Cox regression model

Statistical analysis description:

Second analysis of CPFS: adjusted Cox regression model, including both treatment comparisons and stratification factors (ECOG and randomising centre). Using stratification factors within the design leads to correlation between the treatment groups which, when not adjusted for, can lead to upwards biased standard error rates for treatment effects, CIs which are too wide, type 1 error rates which are too low and a reduction in power. Owning to this conclusions are based on adjusted analysis.

Comparison groups	ZA v No ZA
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.808
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.982
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.845
upper limit	1.141

Notes:

[2] - The use of both log-rank and cox regression models was pre-specified in the protocol.

Primary: Clinical Progression-Free Survival (CPFS) - Sr89 comparison

End point title	Clinical Progression-Free Survival (CPFS) - Sr89 comparison

End point description:

The primary Phase III analysis compared Sr-89 versus no Sr-89 (stratified for ZA use) and ZA versus no ZA (stratified for Sr-89 use) in terms of CPFS. CPFS was defined as the number of whole days from the date of randomisation to the first occurrence of SRE, pain progression or death. Patients not experiencing clinical progression were censored at the date last known to be progression free.

End point type	Primary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	Sr89	No Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	378	379		
Units: Days				
Death	103	106		
SRE	68	61		
Pain	120	144		
Death SRE	0	1		
SRE pain	58	35		

Statistical analyses

Statistical analysis title	Unadjusted, stratified log rank
Comparison groups	No Sr89 v Sr89
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.123 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.03

Notes:

[3] - In total, there were 696 events: 349 (50%) in the Sr-89 group and 347 (50%) in the no Sr-89 group. A stratified log-rank test comparing Sr-89 and no Sr-89 revealed no difference in CPFS between the two groups ($\chi 2 = 2.38$; $p = 0.1230$).

Statistical analysis title	Adjusted Cox proportional hazards model
Comparison groups	No Sr89 v Sr89
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.847
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.729
upper limit	0.985

Primary: Cost-effectiveness ICER per additional QALY - ZA & Sr89

End point title	Cost-effectiveness ICER per additional QALY - ZA & Sr89[4]

End point description:

A total NHS cost and number of QALYs were calculated for each of the 707 patients for whom information on costs and preference-based quality of life (EQ-5D) was available. The mean total cost and mean total QALYs across all patients under a given treatment were calculated. As the distribution of costs and QALYs are typically skewed, 95% confidence intervals around mean values were obtained on the basis of 1000 replications using the bias corrected and accelerated (BCa) bootstrap method. Incremental analysis was carried out to determine the difference in mean total costs and QALYs. These

differences were summarised in an incremental cost-effectiveness ratio (ICER), a measure that reflects the extra cost associated with a gain of one additional QALY.
Full details of the cost effectiveness analysis can be found in the National Institute for Health Research (UK) Health Technology Assessment Program (vol20(53) July 2016) and a separate BJUI 2016 paper by Andronis et al.

End point type	Primary

End point timeframe:

Analysed once all patients had complete follow-up.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Full cost effectiveness analysis was conducted and results were published in the end of trial report published by the NIHR HTA and in a separate journal article in 2016, both listed in the Further information section of this report.

End point values	ZA	Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	707	707		
Units: Pounds Sterling				
number (not applicable)	8005	16590		

Statistical analyses

No statistical analyses for this end point

Secondary: Skeletal-related event-free interval(SREFI) - ZA

End point title	Skeletal-related event-free interval(SREFI) - ZA

End point description:

Skeletal-related event-free interval (SREFI) was defined as the time in whole days from the date of randomisation to the date of the first occurrence of a SRE. A SRE was defined as any one of the following:

- symptomatic pathological bone fracture
- spinal cord or nerve root compression likely to be related to cancer or treatment
- cancer related surgery to bone
- radiation therapy to bone (including use of radioisotopes)
- change of antineoplastic therapy to treat bone pain due to prostate cancer
- hypercalcaemia

Patients who did not experience a SRE were censored at death or the date last known to be alive.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	ZA	No ZA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	381		
Units: Months				
median (confidence interval 95%)	13.6 (11.76 to 16.62)	11.17 (9.76 to 13.01)		

Statistical analyses

Statistical analysis title	Stratified log-rank
Statistical analysis description:	
An unadjusted log rank test comparing ZA with no ZA stratified by Sr89 use.	
Comparison groups	ZA v No ZA
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011 [5]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.95

Notes:

[5] - In total, there were 437 events: 234 (54%) in the no ZA group and 203 (46%) in the ZA group. Stratified log-rank test showed a statistically significant difference in SREFIs between the two groups ($\chi 2 = 6.49$, $p = 0.011$).

Secondary: Skeletal-related event-free interval(SREFI) - Sr89

End point title	Skeletal-related event-free interval(SREFI) - Sr89
End point description:	
As per Skeletal-related event-free survival (SREFS) - ZA	
End point type	Secondary
End point timeframe:	
Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.	

End point values	Sr89	No Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	378	379		
Units: Months				
median (confidence interval 95%)	13.04 (11.14 to 14.69)	11.7 (10.58 to 13.6)		

Statistical analyses

Statistical analysis title	Stratified log-rank

Statistical analysis description:

Unadjusted log rank test comparing Sr89 with no Sr89 stratified by ZA use.

Comparison groups	Sr89 v No Sr89
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.169 [6]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.06

Notes:

[6] - There were 437 events: 222 (51%) in the no Sr-89 group and 215 (49%) in the Sr-89 group. Stratified log-rank test showed no difference in SREFI between the two groups ($\chi 2 = 1.89$; $p = 0.169$).

Secondary: Pain progression-free interval- ZA

End point title	Pain progression-free interval- ZA

End point description:

Pain progression-free interval (PPFI) was defined as the time in whole days from the date of randomisation to the date of clinician-determined pain progression. Patients not experiencing pain progression were censored at the date of death or the date last known to be alive.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	ZA	No ZA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	381		
Units: Months				
median (confidence interval 95%)	12.19 (10.78 to 15.38)	11.76 (10.55 to 13.37)		

Statistical analyses

Statistical analysis title	Stratified log-rank

Statistical analysis description:

A stratified log-rank test comparing ZA with no ZA, stratified by Sr-89.

Comparison groups	ZA v No ZA

Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3127 [7]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.1

Notes:

[7] - There were 432 events: 225 (52%) in the no ZA group and 207 (48%) in the ZA group. A stratified log-rank test was performed comparing ZA with no ZA. No difference in PPFI between the two groups was observed ($\chi 2 = 1.02$; $p = 0.3127$).

Secondary: Pain progression-free interval- Sr89

End point title	Pain progression-free interval- Sr89

End point description:

As per ZA comparison group.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	Sr89	No Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	378	379		
Units: Months				
median (confidence interval 95%)	12.22 (10.94 to 14.09)	11.76 (10.32 to 13.54)		

Statistical analyses

Statistical analysis title	Stratified log-rank

Statistical analysis description:

A stratified log-rank test comparing Sr-89 with no Sr-89, stratified by ZA. Conclusions were based on a two-sided 5% significance level. No adjustments for multiple testing were made.

Comparison groups	Sr89 v No Sr89
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3991 [8]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.11

Notes:

[8] - There were 432 events: 215 (50%) in the no Sr-89 group and 217 (50%) in the Sr-89 group. A stratified log-rank test was performed comparing Sr-89 with no Sr-89. No difference in PPFI between the two groups was observed ($\chi 2 = 0.40$; $p = 0.3991$).

Secondary: Overall survival (OS) -- ZA

End point title	Overall survival (OS) -- ZA

End point description:

Overall survival was defined as the number of whole days from the date of randomisation to the date of death from any cause. Patients alive at the date of analysis were censored at the date last known to be alive.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	ZA	No ZA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	376	381		
Units: Months				
median (confidence interval 95%)	16.99 (16.07 to 19.23)	17.61 (16.1 to 18.96)		

Statistical analyses

Statistical analysis title	Stratified log-rank

Statistical analysis description:

A stratified log-rank comparing ZA with no ZA, stratified by Sr-89, with no adjustments made for multiple testing.

Comparison groups	No ZA v ZA
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.909 [9]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.16

Notes:

[9] - There were 618 events: 309 (50%) occurred in each group. Stratified log-rank test comparing ZA with no ZA demonstrated no difference in OS between the two groups ($\chi 2 = 0.01$; $p = 0.909$).

Secondary: Overall survival (OS) -- Sr89

End point title	Overall survival (OS) -- Sr89

End point description:

As per Overall survival (OS) -- ZA

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	Sr89	No Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	378	379		
Units: Months				
median (confidence interval 95%)	18.17 (16.66 to 19.12)	16.59 (15.61 to 18.27)		

Statistical analyses

Statistical analysis title	Stratified log-rank

Statistical analysis description:

A stratified log rank test comparing Sr89 with No Sr89 stratified by ZA use.

Comparison groups	Sr89 v No Sr89
Number of subjects included in analysis	757
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3359 [10]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.08

Notes:

[10] - There were 618 events: 310 (50%) in the no Sr-89 group and 308 in the Sr-89 (50%) group. Stratified log-rank test comparing Sr-89 with no Sr-89 demonstrated no difference in OS between the two groups ($\chi 2 = 0.93$; $p = 0.3359$).

Secondary: Quality-Adjusted Survival - ZA

End point title	Quality-Adjusted Survival - ZA

End point description:

The integrated quality adjusted survival product is the product of the survival and EQ-5D quality of life measure over the 2 year period of interest. The methodology of integrating QoL and survival was carried

out at the group level. The area under the curve at 2 years gave the mean QALY for each group. Standard errors were calculated and 95% confidence intervals constructed using bootstrapping techniques with 1000 replications.

Full descriptive quality of life data has been published in the Trial report published by the National Institute for Health Research (UK) Health Technology Assessment Program (Vol 20(53) July 2016; ISSN 1366-5278; DOI 10.3310/hta20530)

End point type	Secondary

End point timeframe:

Group based quality adjusted survival analysis conducted to assess the balance between Quality of Life and Survival. As the median survival in the trial was 1.4 years, 2 years was deemed the appropriate cut-off point for the quality adjusted survival.

End point values	ZA	No ZA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Years				
median (confidence interval 95%)	1.04 (0.98 to 1.1)	1 (0.93 to 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality Adjusted Survival - Sr89

End point title	Quality Adjusted Survival - Sr89

End point description:

The integrated quality adjusted survival product is the product of the survival and EQ-5D quality of life measure over the 2 year period of interest. The methodology of integrating QoL and survival was carried out at the group level. The area under the curve at 2 years gave the mean QALY for each group. Standard errors were calculated and 95% confidence intervals constructed using bootstrapping techniques with 1000 replications.

Full descriptive quality of life data has been published in the Trial report published by the National Institute for Health Research (UK) Health Technology Assessment Program (Vol 20(53) July 2016; ISSN 1366-5278; DOI 10.3310/hta20530)

End point type	Secondary

End point timeframe:

Group based quality adjusted survival analysis conducted to assess the balance between Quality of Life and Survival. As the median survival in the trial was 1.4 years, 2 years was deemed the appropriate cut-off point for the quality adjusted survival.

End point values	Sr89	No Sr89		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	350	357		
Units: Years				
median (confidence interval 95%)	1.05 (0.99 to 1.12)	0.97 (0.91 to 1.03)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Enter the time point(s) or time period for adverse events assessment.

Adverse event reporting additional description:

Enter information about the adverse event collection and provide details about the method of assessment and monitoring (e.g. daily questionnaire).

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Arm A

Reporting group description:

Standard care (Docetaxel and prednisolone)

Reporting group title	Arm B

Reporting group description:

Docetaxel, prednisolone and ZA

Reporting group title	Arm C

Reporting group description:

Docetaxel, prednisolone and Sr89

Reporting group title	Arm D

Reporting group description:

Docetaxel, prednisolone, ZA and Sr89

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	84 / 191 (43.98%)	106 / 188 (56.38%)	97 / 190 (51.05%)
number of deaths (all causes)	154	156	155
number of deaths resulting from adverse events	6	4	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy	Additional description: Possibly related to cancer treatment		
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Phlebitis (including superficial thrombosis)			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thrombosis/embolism (Vascular access-related)			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis/thrombus/embolism			
subjects affected / exposed	3 / 191 (1.57%)	3 / 188 (1.60%)	2 / 190 (1.05%)
occurrences causally related to treatment / all	1 / 3	2 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vessel injury-artery			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Intra-operative Injury, Unspecified			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Consitutional symptoms - unspecified			
subjects affected / exposed	3 / 191 (1.57%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	2 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death not associated with CTCAE term			
subjects affected / exposed	1 / 191 (0.52%)	6 / 188 (3.19%)	6 / 190 (3.16%)
occurrences causally related to treatment / all	0 / 1	0 / 6	1 / 6
deaths causally related to treatment / all	0 / 1	0 / 6	1 / 6
Lethargy			
subjects affected / exposed	3 / 191 (1.57%)	2 / 188 (1.06%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	2 / 4	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pain			

subjects affected / exposed	10 / 191 (5.24%)	12 / 188 (6.38%)	14 / 190 (7.37%)
occurrences causally related to treatment / all	0 / 12	1 / 13	2 / 17
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 2
Pain, Unspecified			
subjects affected / exposed	1 / 191 (0.52%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rigors/chills			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	9 / 191 (4.71%)	7 / 188 (3.72%)	5 / 190 (2.63%)
occurrences causally related to treatment / all	6 / 11	5 / 8	2 / 5
deaths causally related to treatment / all	1 / 1	1 / 2	1 / 2
Pneumonitis/pulmonary infiltrates			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary/Upper Respiratory, Unspecified			

subjects affected / exposed	3 / 191 (1.57%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pleural effusion (non-malignant)			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac - General unspecified			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infarction			
subjects affected / exposed	0 / 191 (0.00%)	2 / 188 (1.06%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Hypotension			
subjects affected / exposed	2 / 191 (1.05%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Left ventricular systolic dysfunction			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular and nodal arrhythmia			
subjects affected / exposed	2 / 191 (1.05%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasovagal episode			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			

subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CNS cerebrovascular ischemia			
subjects affected / exposed	2 / 191 (1.05%)	3 / 188 (1.60%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion			
subjects affected / exposed	0 / 191 (0.00%)	2 / 188 (1.06%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mood altered			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurology, Unspecified			
subjects affected / exposed	4 / 191 (2.09%)	3 / 188 (1.60%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy, motor			

subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy, sensory			
subjects affected / exposed	2 / 191 (1.05%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech impairment	Additional description: e.g. dysphasia or aphasia		
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Bone Marrow - unspecified event			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema - limb			
subjects affected / exposed	0 / 191 (0.00%)	2 / 188 (1.06%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Haemoglobin			

subjects affected / exposed	2 / 191 (1.05%)	3 / 188 (1.60%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 2	2 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage, GI			
subjects affected / exposed	1 / 191 (0.52%)	4 / 188 (2.13%)	6 / 190 (3.16%)
occurrences causally related to treatment / all	0 / 1	2 / 4	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haemorrhage, GU			
subjects affected / exposed	0 / 191 (0.00%)	3 / 188 (1.60%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemorrhage, pulmonary/upper respiratory			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	6 / 191 (3.14%)	7 / 188 (3.72%)	8 / 190 (4.21%)
occurrences causally related to treatment / all	6 / 6	7 / 7	9 / 9
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Platelets			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolysis	Additional description: e.g. immune hemolytic anemia, drug-related hemolysis		
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage, Unspecified			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Ocular/Visual, Unspecified			

subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blurred vision			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 191 (0.52%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	5 / 191 (2.62%)	3 / 188 (1.60%)	6 / 190 (3.16%)
occurrences causally related to treatment / all	5 / 5	2 / 3	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever	Additional description: In the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L		
subjects affected / exposed	11 / 191 (5.76%)	7 / 188 (3.72%)	13 / 190 (6.84%)
occurrences causally related to treatment / all	9 / 14	7 / 10	9 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal - unspecified event			
subjects affected / exposed	2 / 191 (1.05%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nausea			

subjects affected / exposed	2 / 191 (1.05%)	3 / 188 (1.60%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	1 / 2	2 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 191 (1.05%)	2 / 188 (1.06%)	4 / 190 (2.11%)
occurrences causally related to treatment / all	1 / 2	2 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis/stomatitis (clinical exam)			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatology/Skin - Unspecified event			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction/extravasation changes			
subjects affected / exposed	1 / 191 (0.52%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound complication, non-infectious			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Fistula, GU			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GU			
subjects affected / exposed	0 / 191 (0.00%)	2 / 188 (1.06%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 191 (0.52%)	5 / 188 (2.66%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal/Genitourinary, Unspecified			
subjects affected / exposed	2 / 191 (1.05%)	3 / 188 (1.60%)	2 / 190 (1.05%)
occurrences causally related to treatment / all	2 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stenosis, GU	Additional description: including anastomotic		
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention (including neurogenic bladder)			
subjects affected / exposed	0 / 191 (0.00%)	6 / 188 (3.19%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 6	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urine colour change			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Extremity-lower (Gait/Walking)			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	2 / 191 (1.05%)	4 / 188 (2.13%)	5 / 190 (2.63%)
occurrences causally related to treatment / all	1 / 2	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Muscle weakness, generalized or specific area	Additional description: Not due to neuropathy		
subjects affected / exposed	5 / 191 (2.62%)	4 / 188 (2.13%)	2 / 190 (1.05%)
occurrences causally related to treatment / all	1 / 5	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Musculoskeletal/Soft Tissue, Unspecified			
subjects affected / exposed	2 / 191 (1.05%)	1 / 188 (0.53%)	3 / 190 (1.58%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis	Additional description: Inflammation/damage of muscle		
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis (avascular necrosis)			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Febrile neutropenia	Additional description: Fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		
subjects affected / exposed	10 / 191 (5.24%)	9 / 188 (4.79%)	14 / 190 (7.37%)
occurrences causally related to treatment / all	10 / 10	9 / 9	14 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils	Additional description: (ANC <1.0 x 10e9/L)		
subjects affected / exposed	10 / 191 (5.24%)	7 / 188 (3.72%)	2 / 190 (1.05%)
occurrences causally related to treatment / all	9 / 10	7 / 7	2 / 2
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Infection, Unspecified			

subjects affected / exposed	0 / 191 (0.00%)	6 / 188 (3.19%)	5 / 190 (2.63%)
occurrences causally related to treatment / all	0 / 0	4 / 6	4 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infection with normal ANC or Grade 1 or 2 neutrophils			
subjects affected / exposed	5 / 191 (2.62%)	6 / 188 (3.19%)	5 / 190 (2.63%)
occurrences causally related to treatment / all	3 / 5	3 / 6	5 / 6
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Infection with unknown ANC			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypocalcaemia			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine blood test abnormality			
subjects affected / exposed	0 / 191 (0.00%)	1 / 188 (0.53%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic/Laboratory, Unspecified			
subjects affected / exposed	0 / 191 (0.00%)	0 / 188 (0.00%)	1 / 190 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 191 (0.52%)	0 / 188 (0.00%)	0 / 190 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm D		
Total subjects affected by serious adverse events			
subjects affected / exposed	86 / 188 (45.74%)		
number of deaths (all causes)	153		
number of deaths resulting from adverse events	8		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy	Additional description: Possibly related to cancer treatment		
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Phlebitis (including superficial thrombosis)			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis/embolism (Vascular access-related)			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Thrombosis/thrombus/embolism			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Vessel injury-artery			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Surgical and medical procedures			
Intra-operative Injury, Unspecified			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Consitutional symptoms - unspecified				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Death not associated with CTCAE term				
subjects affected / exposed	5 / 188 (2.66%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 5			
Lethargy				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pain				
subjects affected / exposed	10 / 188 (5.32%)			
occurrences causally related to treatment / all	4 / 10			
deaths causally related to treatment / all	1 / 1			
Pain, Unspecified				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Rigors/chills				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Allergic reaction/hypersensitivity (including drug fever)				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				

subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 188 (2.66%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Pneumonitis/pulmonary infiltrates				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary/Upper Respiratory, Unspecified				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion (non-malignant)				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiac - General unspecified				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Infarction				
subjects affected / exposed	3 / 188 (1.60%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	2 / 3			
Hypotension				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Left ventricular systolic dysfunction				

subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular and nodal arrhythmia				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vasovagal episode				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
CNS cerebrovascular ischemia				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cognitive disorder				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Confusion				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Memory impairment				

subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mood altered				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neurology, Unspecified				
subjects affected / exposed	4 / 188 (2.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Neuropathy, motor				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neuropathy, sensory				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Speech impairment	Additional description: e.g. dysphasia or aphasia			
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Bone Marrow - unspecified event				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Disseminated intravascular coagulation				

subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema - limb				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Haematoma				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Haemorrhage, GI				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haemorrhage, GU				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemorrhage, pulmonary/upper respiratory				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophils/granulocytes (ANC/AGC)				
subjects affected / exposed	8 / 188 (4.26%)			
occurrences causally related to treatment / all	9 / 9			
deaths causally related to treatment / all	0 / 0			
Platelets				

subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemolysis	Additional description: e.g. immune hemolytic anemia, drug-related hemolysis		
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Haemorrhage, Unspecified			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ocular/Visual, Unspecified			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blurred vision			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			

subjects affected / exposed	5 / 188 (2.66%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	1 / 1			
Fever	Additional description: In the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L			
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal - unspecified event				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcer				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 188 (1.60%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Mucositis/stomatitis (clinical exam)				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Obstruction				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Dermatology/Skin - Unspecified event				

subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injection site reaction/extravasation changes				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound complication, non-infectious				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Fistula, GU				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction, GU				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Renal/Genitourinary, Unspecified				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stenosis, GU	Additional description: including anastomotic			
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention (including neurogenic bladder)				

subjects affected / exposed	4 / 188 (2.13%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Urine colour change				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Extremity-lower (Gait/Walking)				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Muscle weakness, generalized or specific area	Additional description: Not due to neuropathy			
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal/Soft Tissue, Unspecified				
subjects affected / exposed	2 / 188 (1.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myositis	Additional description: Inflammation/damage of muscle			
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteonecrosis (avascular necrosis)				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Febrile neutropenia	Additional description: Fever of unknown origin without clinically or microbiologically documented infection (ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		
subjects affected / exposed	9 / 188 (4.79%)		
occurrences causally related to treatment / all	9 / 10		
deaths causally related to treatment / all	0 / 0		
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils	Additional description: (ANC <1.0 x 10e9/L)		
subjects affected / exposed	4 / 188 (2.13%)		
occurrences causally related to treatment / all	2 / 4		
deaths causally related to treatment / all	0 / 0		
Infection, Unspecified			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infection with normal ANC or Grade 1 or 2 neutrophils			
subjects affected / exposed	6 / 188 (3.19%)		
occurrences causally related to treatment / all	4 / 7		
deaths causally related to treatment / all	1 / 1		
Infection with unknown ANC			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	5 / 188 (2.66%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Creatinine blood test abnormality			

subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic/Laboratory, Unspecified			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 191 (42.41%)	72 / 188 (38.30%)	76 / 190 (40.00%)
Nervous system disorders			
Sensory neuropathy			
subjects affected / exposed	3 / 191 (1.57%)	1 / 188 (0.53%)	5 / 190 (2.63%)
occurrences (all)	3	1	7
Blood and lymphatic system disorders			
Oedema peripheral			
subjects affected / exposed	5 / 191 (2.62%)	4 / 188 (2.13%)	5 / 190 (2.63%)
occurrences (all)	7	4	5
Haemoglobin			
subjects affected / exposed	5 / 191 (2.62%)	9 / 188 (4.79%)	7 / 190 (3.68%)
occurrences (all)	6	15	11
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	8 / 191 (4.19%)	7 / 188 (3.72%)	10 / 190 (5.26%)
occurrences (all)	12	7	12
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 191 (5.76%)	13 / 188 (6.91%)	17 / 190 (8.95%)
occurrences (all)	14	14	23

Pain			
subjects affected / exposed	23 / 191 (12.04%)	13 / 188 (6.91%)	22 / 190 (11.58%)
occurrences (all)	35	23	31
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 191 (3.66%)	4 / 188 (2.13%)	7 / 190 (3.68%)
occurrences (all)	7	4	7
Nausea			
subjects affected / exposed	7 / 191 (3.66%)	4 / 188 (2.13%)	2 / 190 (1.05%)
occurrences (all)	10	5	2
Vomiting			
subjects affected / exposed	6 / 191 (3.14%)	4 / 188 (2.13%)	1 / 190 (0.53%)
occurrences (all)	6	4	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 191 (3.66%)	3 / 188 (1.60%)	2 / 190 (1.05%)
occurrences (all)	8	3	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	4 / 191 (2.09%)	4 / 188 (2.13%)	4 / 190 (2.11%)
occurrences (all)	4	7	6
Renal and urinary disorders			
Urinary frequency/urgency			
subjects affected / exposed	0 / 191 (0.00%)	3 / 188 (1.60%)	1 / 190 (0.53%)
occurrences (all)	0	4	1
Infections and infestations			
Febrile neutropenia			
subjects affected / exposed	10 / 191 (5.24%)	6 / 188 (3.19%)	7 / 190 (3.68%)
occurrences (all)	15	8	8
Infection	Additional description: Unknown ANC		
subjects affected / exposed	4 / 191 (2.09%)	5 / 188 (2.66%)	7 / 190 (3.68%)
occurrences (all)	5	5	7
Metabolism and nutrition disorders			
Alkaline phosphatase			
subjects affected / exposed	3 / 191 (1.57%)	4 / 188 (2.13%)	6 / 190 (3.16%)
occurrences (all)	4	8	9

Non-serious adverse events	Arm D		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 188 (38.83%)		
Nervous system disorders			
Sensory neuropathy			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Oedema peripheral			
subjects affected / exposed	4 / 188 (2.13%)		
occurrences (all)	10		
Haemoglobin			
subjects affected / exposed	8 / 188 (4.26%)		
occurrences (all)	16		
Neutrophils/granulocytes (ANC/AGC)			
subjects affected / exposed	8 / 188 (4.26%)		
occurrences (all)	8		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	10 / 188 (5.32%)		
occurrences (all)	12		
Pain			
subjects affected / exposed	16 / 188 (8.51%)		
occurrences (all)	25		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 188 (2.66%)		
occurrences (all)	6		
Nausea			
subjects affected / exposed	4 / 188 (2.13%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	3 / 188 (1.60%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	0 / 188 (0.00%) 0		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	2 / 188 (1.06%) 2		
Renal and urinary disorders Urinary frequency/urgency subjects affected / exposed occurrences (all)	4 / 188 (2.13%) 4		
Infections and infestations Febrile neutropenia subjects affected / exposed occurrences (all)	6 / 188 (3.19%) 6		
Infection subjects affected / exposed occurrences (all)	Additional description: Unknown ANC 4 / 188 (2.13%) 5		
Metabolism and nutrition disorders Alkaline phosphatase subjects affected / exposed occurrences (all)	3 / 188 (1.60%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2005	PHASE II PROTOCOL • Change to the eligibility criteria to enable patients to enter the study without the need for a confirmation prostate biopsy if they have confirmed bone disease with a PSA value > 100ng/ml. • Change to wording of baseline and post chemotherapy assessment requirements will allow centres to take part in the study without the need to perform clinical procedures if local facilities are not available.
07 June 2005	• Safety amendment to clarification of zoledronic acid dose procedures to comply with SmPC.
04 May 2007	• Changes to the inclusion criteria clarified patient eligibility regarding abnormal ALT and AST levels. • The requirement for a confirmed Serum Testosterone blood test was removed from the screening procedures. • A new entry criteria question was added to ensure that at time of study entry all patients were fit enough to receive any of the trial treatments, in the opinion of the investigator. • Clarification of administration sequence of trial treatments.
24 September 2008	PHASE III PROTOCOL • The majority of the changes related to the transition from a phase II to a phase III clinical trial, covering trial infrastructure, data collection procedures and statistical considerations. These changes had no direct impact on patient participation or safety, but did increase the maximum number of chemotherapy cycles from 6 to10, according to NICE guidelines for docetaxel chemotherapy.
12 April 2011	• This amendment concerns a statistical redesign of the phase III trial from a 4 arm comparison to a 2 by 2 factorial design to assess treatment efficacy. • Reduction of target recruitment from 1240 (as per version 8 amendment) to 618 evaluable patients. The trial will close to recruitment at the end of February 2012.
25 May 2011	• This amendment concerns a correction in section 12.2.3 on timing of analysis. We intend to conduct initial analysis once all patients have at least 1 year's follow-up not 2 years as previously stated.
17 February 2012	Substantial amendments : • Changing the requirement for both ALT and AST to be tested – only one of them needs to have been performed. • Change of definition for skeletal related event-free interval and pain progression-free interval, and removal of the event of death as a skeletal related event and element of pain progression criteria. Non-substantial amendments : • Clarification of prophylactic anti-emetic for nausea/vomiting due to chemotherapy, and permission to use local protocols that coincide with off-study practice. • Additional safety information for zoledronic acid administration. • Updating of Deputy Clinical Co-ordinators details.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Describe any significant limitations of the trial (e.g. early termination leading to a small number of subjects analysed; technical problems with measurement leading to unreliable, or uninterpretable data).

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27434595

http://www.ncbi.nlm.nih.gov/pubmed/26794729

http://www.ncbi.nlm.nih.gov/pubmed/27256016