Clinical trial results:
A Phase 3 Study to Evaluate the Efficacy and Safety of Docetaxel and Prednisone with or without Lenalidomide in Subjects with Castrate-Resistant Prostate Cancer (CRPC)

Summary

EudraCT number	2008-007969-23
Trial protocol	BE HU CZ DE GB AT NL IT ES DK SE GR
Global end of trial date	28 November 2016

Results information

Result version number	v1 (current)
This version publication date	14 December 2017
First version publication date	14 December 2017

Trial information

Trial identification

Sponsor protocol code	CC-5013-PC-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00988208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	ClinicalTrialDisclosure, Celgene Corporation, +1 8882601599, ClinicalTrialDisclosure@celgene.com
Scientific contact	Ileana Elias, MD, Celgene Corporation, +1 647-948-4300, IlElias@Celgene.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 November 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare the Overall Survival (OS) benefit of docetaxel and prednisone with and without lenalidomide as first-line therapy in chemo-naïve metastatic CRPC subjects

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 52
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Denmark: 26
Country: Number of subjects enrolled	France: 110
Country: Number of subjects enrolled	Germany: 63
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 58
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Netherlands: 75
Country: Number of subjects enrolled	Poland: 55
Country: Number of subjects enrolled	Russian Federation: 72
Country: Number of subjects enrolled	South Africa: 27
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	Sweden: 15

Country: Number of subjects enrolled	United Kingdom: 83
Country: Number of subjects enrolled	United States: 275
Worldwide total number of subjects	1059
EEA total number of subjects	646

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)	334
From 65 to 84 years	712
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Following a safety and efficacy data review by the Data Monitoring Committee(DMC), the trial was stopped for futility. At that time, 1059 participants had been randomized and 1046 treated with either lenalidomide plus docetaxel and prednisone or placebo plus docetaxel and prednisone. A data cutoff date of 13 January 2012 was established.

Pre-assignment

Screening details:

Participants who had started a treatment cycle at the time of termination request were allowed to complete the cycle and have their discontinuation visit at the next cycle (21 days later). The safety follow-up of 28 days was also added to ensure all adverse events were followed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Docetaxel/Prednisone/Placebo (DP)

Arm description:

Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day (BID) and identically matching placebo capsules daily (QD) on Days 1-14 in each 21-day treatment cycle.

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

Dosage and administration details:

Docetaxel 75 mg/m^2 by intravenous administration on Day 1 of each 21-day treatment cycle

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

Dosage and administration details:

Identically matching placebo capsules daily (QD) on days 1-14 of each 21-day treatment cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	Deltasone; Sterapred; Rayos; Prednicot
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg tablets twice a day (BID) in each 21-day treatment cycle.

Arm title	Docetaxel/Prednisone/Lenalidomide (DPL)

Arm description:

Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day and lenalidomide 25 mg capsules daily (QD) on days 1-14 in each

21-day treatment cycle.

Arm type	Experimental
Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	CC-5013
Other name	Revlimid®
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Lenalidomide 25 mg capsules QD on days 1-14 of each 21-day treatment cycle.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	Deltasone Sterapred Rayos Prednicot
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone 5 mg tablets twice a day in each 21-day treatment cycle.

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	Taxotere
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel 75 mg/m^2 by intravenous administration on Day 1 of each 21-day treatment cycle

Number of subjects in period 1	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)
Started	526	533
Treated	521	525
Completed	95	95
Not completed	431	438
Adverse event, serious fatal	9	15
Consent withdrawn by subject	50	57
Clinical Deterioration	7	14
Subject decision/investigator discretion	32	32
Adverse event, non-fatal	71	122
Sponsor Decision	102	78
Biochemical Progression	21	7
Unspecified	8	3
Lost to follow-up	2	3
Clinical Progression	17	16
Disease Progression	103	89

Protocol deviation	9	2

Baseline characteristics

Reporting groups	
Reporting group title	Docetaxel/Prednisone/Placebo (DP)
Reporting group description:	
Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day (BID) and identically matching placebo capsules daily (QD) on Days 1-14 in each 21-day treatment cycle.	
Reporting group title	Docetaxel/Prednisone/Lenalidomide (DPL)
Reporting group description:	
Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day and lenalidomide 25 mg capsules daily (QD) on days 1-14 in each 21-day treatment cycle.	

Reporting group values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)	Total
Number of subjects	526	533	1059
Age Categorical			
Units: Subjects			
< 65 years	171	163	334
> = 65 years to < = 75 years	246	244	490
> 75 years	109	126	235
Age Continuous			
Units: years			
arithmetic mean	68.4	68.9	
standard deviation	± 7.79	± 7.98	-
Gender Categorical			
Units: Subjects			
Female	0	0	0
Male	526	533	1059
Region of Enrollment			
Rest of World includes Israel, Russia, Mexico and South Africa			
Units: Subjects			
US or Canada	136	140	276
EU or Australia	329	330	659
Rest of World (Includes 4 additional countries)	61	63	124
Race, Customized			
Units: Subjects			
White	433	436	869
Other or no answer	55	67	122
Black or African American	25	21	46
Asian	8	6	14
American Indian or Alaska Native	5	3	8
Body Mass Index, Categorical			
Units: Subjects			
< 25 kg/m^2	134	138	272
25-30 kg/m^2	221	243	464
>30 kg/m^2	171	152	323
ECOG Performance Status			

Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living activities of the patient and determine appropriate treatment and prognosis.			
Units: Subjects			
0 (Fully Active)	257	252	509
1 (Restrictive but ambulatory)	247	256	503
2 (Ambulatory but unable to work)	21	24	45
3 (Limited self-care)	1	0	1
Not specified	0	1	1
Type of Disease Progression			
Categories of specific indicators of disease progression type			
Units: Subjects			
Rising PSA only	146	159	305
Radiographic progression	380	374	754
Prior Radiotherapy			
Participants who had been treated with prior radiation therapy			
Units: Subjects			
Previous Prior Radiotherapy	308	312	620
No Previous Prior Radiotherapy	218	221	439
Prior Cancer Surgery			
Participants who had undergone a surgical procedure associated with their prostate cancer diagnosis prior to study participation			
Units: Subjects			
Previous Cancer Surgery	335	358	693
No previous cancer surgery	191	175	366
Other Prior Anti-Cancer Therapy			
Participants who were treated with other types of anti-cancer therapies prior to participation in study			
Units: Subjects			
Received prior anti-cancer therapy	79	71	150
Did not receive prior anti-cancer therapy	447	462	909
Metastatic Sites of Disease Outside of Prostate			
Specific sites of the body that have advanced spread of the prostate cancer.			
Units: Subjects			
Bone only	157	169	326
Soft tissues only	94	104	198
Both bone and Soft tissues	273	259	532
None	2	1	3
Study Specific Characteristic | Weight			
Units: kilograms			
arithmetic mean	86.4	86	
standard deviation	± 16.18	± 15.70	-
Study Specific Characteristic | Height			
Units: centimeters			
arithmetic mean	174.0	174.4	
standard deviation	± 7.81	± 7.38	-
Study Specific Characteristic | Body Mass Index			
BMI or body mass index is a statistical benchmark that compares an individual’s height and weight.			
Units: (kg/m^2)			
arithmetic mean	28.6	28.3	
standard deviation	± 5.02	± 4.60	-

Study Specific Characteristic | Baseline PSA (Prostate Specific Antigen) levels			
Prostate-specific antigen (PSA) is a substance produced by the prostate gland. Elevated PSA levels may indicate prostate cancer or a noncancerous condition such as prostatitis or an enlarged prostate.			
Units: (ng/ml)			
arithmetic mean	290.359	316.501	
standard deviation	± 659.1583	± 776.1133	-

End points

End points reporting groups

Reporting group title	Docetaxel/Prednisone/Placebo (DP)
Reporting group description:	
Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day (BID) and identically matching placebo capsules daily (QD) on Days 1-14 in each 21-day treatment cycle.	
Reporting group title	Docetaxel/Prednisone/Lenalidomide (DPL)
Reporting group description:	
Participants received docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, prednisone 5 mg orally twice a day and lenalidomide 25 mg capsules daily (QD) on days 1-14 in each 21-day treatment cycle.	

Primary: Kaplan Meier Estimate for Overall Survival (OS)

End point title	Kaplan Meier Estimate for Overall Survival (OS)
End point description:	
Overall survival (OS) was the time from the date of randomization to the date of death from any cause. If no death was reported for a participant before the cut-off date for OS analysis, OS was censored at the last date at which the participant was alive. Intention-to-Treat population (ITT), defined as all randomized subjects irrespective of whether they received treatment or not.	
End point type	Primary
End point timeframe:	
From randomization until death from any cause up to the data cut-off date of 13 January 2012; approximately 26 months	

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526[1]	533		
Units: weeks				
median (confidence interval 95%)	99999 (75.71 to 999999)	77 (64.29 to 81.71)		

Notes:

[1] - Median OS was not reached for the DP arm; only 92 subjects had died at the time of the data cut off

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Docetaxel/Prednisone/Placebo (DP) v Docetaxel/Prednisone/Lenalidomide (DPL)
Number of subjects included in analysis	1059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0017 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.53

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.17
upper limit	2

Notes:

[2] - p-value is based on unstratified log-rank test

Secondary: Kaplan Meier Estimates of Progression-Free Survival (PFS)

End point title	Kaplan Meier Estimates of Progression-Free Survival (PFS)

End point description:

PFS was the time from randomization to disease progression, or death, whatever occurred first. Progression criteria was met by analysis of target and non-target lesions as defined by RECIST Version 1.1 criteria. Progressive Disease (PD) was defined as at least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters while on study or the appearance of one or more new lesions; an increase of at least 5mm as a total sum. Lymph nodes identified as target lesions (≥ 15 mm diameter in short axis) were followed and reported by changes in diameter of short axis; or the unequivocal progression of a non-target lesion defined as an increase in the overall disease burden based on the change in non-measurable disease that is comparable in scope to the increase required to declare PD for measurable disease; 2 or more new bone lesions detected by bone scan. ITT population.

End point type	Secondary

End point timeframe:

From randomization until disease progression or death from any cause; up to the cut-off date of 13 Jan 2012; maximum time on study was approximately 26 months

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	533		
Units: Weeks				
median (confidence interval 95%)	46 (42.14 to 53.57)	45 (38.0 to 46.14)		

Statistical analyses

Statistical analysis title	Statisitical Analysis 1
Comparison groups	Docetaxel/Prednisone/Placebo (DP) v Docetaxel/Prednisone/Lenalidomide (DPL)
Number of subjects included in analysis	1059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0187
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.66

Secondary: Percentage of Participants with an Objective Response According to Response Evaluation Criteria in Solid Tumors - RECIST Version 1.1 criteria

End point title	Percentage of Participants with an Objective Response According to Response Evaluation Criteria in Solid Tumors - RECIST Version 1.1 criteria

End point description:

Objective response (OR) = having a complete response (CR) or partial response (PR) as best overall response. Response Evaluation Criteria in Solid Tumors (RECIST) Criteria 1.1 was defined a CR = Disappearance of all target lesions except lymph nodes (LN); LN must have a decrease in the short axis to <10mm; PR = 30% decrease in sum of diameters of target lesions taking as reference the baseline sum diameters; Progressed Disease (PD) = 20% increase in sum of diameters of target lesions taking as a reference the smallest sum of diameters and an absolute increase of ≥5 mm; the appearance of ≥1 new lesions; Stable Disease (SD)= Neither shrinkage to qualify for PR nor increase in lesions. For non-target lesions a CR = Disappearance of all non-target lesions and all LN must be non-pathological in size <10 mm; Non-CR/Non PD: persistence of one or more non-target lesions; PD = unequivocal progression of existing non-target lesions or appearance of new ones. ITT population.

End point type	Secondary

End point timeframe:

From day 1 to the data cut-off date of 13 January 2012; maximum time on study was approximately 26 months

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	526	533		
Units: percentage of participants				
number (not applicable)	24.3	22.1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Docetaxel/Prednisone/Placebo (DP) v Docetaxel/Prednisone/Lenalidomide (DPL)
Number of subjects included in analysis	1059
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3975
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	0.884

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.665
upper limit	1.176

Secondary: Number of Participants with Treatment Emergent Adverse Events (AEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (AEs)

End point description:

A TEAE is defined as any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose of study drug. A TESAE is defined as any serious adverse event (SAE) occurring or worsening on or after the first dose of study drug and within 28 days after the last dose of study drug. Safety and severity was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0; Severity of AEs were graded (including second primary malignancies) as Grade 1- Mild; Grade 2- Moderate; Grade 3- Severe; Grade 4- Life-threatening; Grade 5-Fatal; Safety Population.

End point type	Secondary

End point timeframe:

From the time from of first dose of study drug administration to 28 days after the last dose of study drug and up to the data cut off date of 13 January 2012; the maximum duration of study drug was 93 weeks for DP and 90.6 weeks for DPL

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	525		
Units: participants				
Any TEAE	512	517		
Any TEAE related to lenalidomide or placebo	379	412		
Any TEAE related to docetaxel/prednisone	475	481		
Any severity grade 3-4 TEAE	303	381		
Any serious AE (SAE)	171	279		
Any SAE related to lenalidomide or placebo	62	167		
Any SAE related to docetaxel/prednisone	86	182		
Any AE causing discontinuation of lenalidomide/PBO	82	150		
Any AE causing withdrawal of docetaxel/prednisone	127	169		
Any TEAE leading to death	16	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Received Post-Study Therapies

End point title	Percentage of Participants Who Received Post-Study Therapies

End point description:

Percentage of Subjects Who Received Post-Study Therapies for advanced Prostate Cancer.

End point type	Secondary

End point timeframe:

The date when the first consent form was signed to the last date of AE data collection; up to the date of the final data analysis date of 20 April 2017

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	525		
Units: percentage of participants				
number (not applicable)	70.8	69.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Secondary Primary Malignancies During the Course of the Trial

End point title	Percentage of Participants with Secondary Primary Malignancies During the Course of the Trial

End point description:

Second primary malignancies were monitored as events of interest and reported as serious adverse events throughout the course of the trial. Safety population.

End point type	Secondary

End point timeframe:

The date when the first consent form was signed to the last date of AE data collection; up to the date of the final data analysis date of 30 November 2016; 7 years and 19 days

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	525		
Units: percentage of participants				
number (not applicable)				
Invasive Secondary Primary Malignancies	1.3	1.7		

Non-Invasive Secondary Primary Malignancies	0.4	1.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Secondary Primary Malignancies

End point title	Time to Onset of Secondary Primary Malignancies

End point description:

The time to the onset of secondary primary malignancies were considered events of interest. Includes the safety population.

End point type	Secondary

End point timeframe:

The date when the first consent form was signed to the last date of AE data collection; up to the date of the final data analysis date of 30 November 2016; 7 years and 19 days

End point values	Docetaxel/Prednisone/Placebo (DP)	Docetaxel/Prednisone/Lenalidomide (DPL)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	521	525		
Units: months				
median (full range (min-max))	29.7 (0.6 to 48.7)	19.7 (3.7 to 65.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment to 28 days after the last dose; as of the final analysis cut-off of 20 April 2017; median overall duration of treatment was 22.1 months for DPL and 27.0 months for the DP group.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	DPL: Docetaxel/ Prednisone/Lenalidomide

Reporting group description:

Participants received Docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, Prednisone 5 mg orally twice a day (BID) and Lenalidomide 25 mg capsules daily (QD) on Days 1-14 in each 21-day treatment cycle.

Reporting group title	DP: Docetaxel/ Prednisone/ Placebo

Reporting group description:

Participants received Docetaxel 75 mg/m^2 by intravenous (IV) administration over 60 minutes on Day 1, Prednisone 5 mg orally twice a day (BID) and identically matching placebo capsules daily (QD) on Days 1-14 in each 21-day treatment cycle.

Serious adverse events	DPL: Docetaxel/ Prednisone/Lenalidomide	DP: Docetaxel/ Prednisone/ Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	283 / 525 (53.90%)	176 / 521 (33.78%)	
number of deaths (all causes)	24	22	
number of deaths resulting from adverse events	7	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
COLON CANCER METASTATIC			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTIC LYMPHOMA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTATIC PAIN			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SQUAMOUS CELL CARCINOMA OF SKIN			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPERFICIAL SPREADING MELANOMA STAGE I			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THYROID CANCER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
ARTERIAL THROMBOSIS LIMB			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEEP VEIN THROMBOSIS			
subjects affected / exposed	13 / 525 (2.48%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	12 / 14	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATOMA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	8 / 525 (1.52%)	7 / 521 (1.34%)	
occurrences causally related to treatment / all	1 / 8	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL ISCHAEMIA			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOPHLEBITIS			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENA CAVA THROMBOSIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENOUS THROMBOSIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	5 / 525 (0.95%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	2 / 6	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
CHILLS			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEATH			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DEVICE OCCLUSION			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	4 / 525 (0.76%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAIT DISTURBANCE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	11 / 525 (2.10%)	5 / 521 (0.96%)	
occurrences causally related to treatment / all	4 / 11	2 / 7	
deaths causally related to treatment / all	0 / 5	1 / 4	
GENERALISED OEDEMA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MALAISE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MULTI-ORGAN FAILURE			

subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
NON-CARDIAC CHEST PAIN			
subjects affected / exposed	4 / 525 (0.76%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERFORMANCE STATUS DECREASED			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	19 / 525 (3.62%)	6 / 521 (1.15%)	
occurrences causally related to treatment / all	12 / 20	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS IN DEVICE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	3 / 525 (0.57%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	5 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

PELVIC PAIN			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
PENILE HAEMORRHAGE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
ACUTE RESPIRATORY FAILURE			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
ALVEOLITIS ALLERGIC			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHMA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
BRONCHOSPASM			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			

subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
COUGH			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA			
subjects affected / exposed	13 / 525 (2.48%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	6 / 13	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPISTAXIS			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	3 / 525 (0.57%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG DISORDER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	3 / 525 (0.57%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	34 / 525 (6.48%)	8 / 521 (1.54%)	
occurrences causally related to treatment / all	31 / 36	7 / 8	
deaths causally related to treatment / all	2 / 2	1 / 1	
PULMONARY FIBROSIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HYPERTENSION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SLEEP APNOEA SYNDROME			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMPLETED SUICIDE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
DELIRIUM			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD CREATININE INCREASED			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD UREA INCREASED			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERNATIONAL NORMALISED RATIO INCREASED			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TROPONIN INCREASED			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINE OUTPUT DECREASED			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
ACCIDENTAL OVERDOSE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FIBULA FRACTURE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FOOT FRACTURE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFUSION RELATED REACTION			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
JOINT DISLOCATION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE RUPTURE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIB FRACTURE			

subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TIBIA FRACTURE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRAUMATIC LIVER INJURY			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 525 (0.19%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
ANGINA PECTORIS			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANGINA UNSTABLE			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARRHYTHMIA			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	14 / 525 (2.67%)	8 / 521 (1.54%)	
occurrences causally related to treatment / all	8 / 16	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL TACHYCARDIA			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL THROMBOSIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIOVENTRICULAR BLOCK COMPLETE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRADYCARDIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
CARDIAC FAILURE CONGESTIVE			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIO-RESPIRATORY ARREST			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
CARDIOGENIC SHOCK			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
CARDIOVASCULAR DISORDER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
CORONARY ARTERY DISEASE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY OCCLUSION			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIASTOLIC DYSFUNCTION			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DILATATION VENTRICULAR			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MYOCARDIAL INFARCTION			
subjects affected / exposed	3 / 525 (0.57%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
PALPITATIONS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERICARDIAL EFFUSION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RIGHT VENTRICULAR FAILURE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYARRHYTHMIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TACHYCARDIA PAROXYSMAL			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VENTRICULAR EXTRASYSTOLES			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CAROTID ARTERY OCCLUSION			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAROTID ARTERY STENOSIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 525 (0.19%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
DIZZINESS			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSKINESIA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOAESTHESIA			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ISCHAEMIC STROKE			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
LACUNAR INFARCTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARKINSON'S DISEASE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PRESYNCOPE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCIATICA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL CORD COMPRESSION			
subjects affected / exposed	1 / 525 (0.19%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	8 / 525 (1.52%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	3 / 9	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	5 / 525 (0.95%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TREMOR			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	18 / 525 (3.43%)	12 / 521 (2.30%)	
occurrences causally related to treatment / all	19 / 27	8 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
subjects affected / exposed	52 / 525 (9.90%)	23 / 521 (4.41%)	
occurrences causally related to treatment / all	59 / 60	27 / 27	
deaths causally related to treatment / all	0 / 0	1 / 1	
LEUKOPENIA			
subjects affected / exposed	5 / 525 (0.95%)	6 / 521 (1.15%)	
occurrences causally related to treatment / all	5 / 5	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			

subjects affected / exposed	32 / 525 (6.10%)	11 / 521 (2.11%)	
occurrences causally related to treatment / all	34 / 35	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	4 / 525 (0.76%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOTIC THROMBOCYTOPENIC PURPURA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
MENIERE'S DISEASE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 525 (0.38%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL FISTULA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

ANAL HAEMORRHAGE			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ULCER			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS ISCHAEMIC			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	4 / 525 (0.76%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	22 / 525 (4.19%)	5 / 521 (0.96%)	
occurrences causally related to treatment / all	18 / 23	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA HAEMORRHAGIC			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULUM			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DUODENAL ULCER HAEMORRHAGE			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROVESICAL FISTULA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FAECALOMA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL HERNIA, OBSTRUCTIVE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC HAEMORRHAGE			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL PERFORATION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROINTESTINAL ULCER HAEMORRHAGE			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATEMESIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTESTINAL INFARCTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
INTESTINAL OBSTRUCTION			
subjects affected / exposed	3 / 525 (0.57%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
INTESTINAL PERFORATION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LARGE INTESTINE PERFORATION			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MELAENA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			

subjects affected / exposed	4 / 525 (0.76%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OESOPHAGEAL ULCER			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
subjects affected / exposed	2 / 525 (0.38%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	1 / 3	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
RETROPERITONEAL HAEMATOMA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBILEUS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			

subjects affected / exposed	8 / 525 (1.52%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	5 / 9	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLECYSTITIS ACUTE			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHOLELITHIASIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GALLBLADDER PERFORATION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERBILIRUBINAEMIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS EXFOLIATIVE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN EXFOLIATION			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
CALCULUS URETHRAL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS HAEMORRHAGIC			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSURIA			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMATURIA			
subjects affected / exposed	5 / 525 (0.95%)	9 / 521 (1.73%)	
occurrences causally related to treatment / all	0 / 6	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDRONEPHROSIS			
subjects affected / exposed	0 / 525 (0.00%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEPHROLITHIASIS			
subjects affected / exposed	0 / 525 (0.00%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			

subjects affected / exposed	10 / 525 (1.90%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	4 / 11	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
RENAL INJURY			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETERIC OBSTRUCTION			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETHRAL OBSTRUCTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY RETENTION			
subjects affected / exposed	3 / 525 (0.57%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ARTHRITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BACK PAIN			
subjects affected / exposed	5 / 525 (0.95%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
subjects affected / exposed	1 / 525 (0.19%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
BURSITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FISTULA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FLANK PAIN			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	1 / 525 (0.19%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEONECROSIS OF JAW			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			

subjects affected / exposed	3 / 525 (0.57%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PATHOLOGICAL FRACTURE			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL OSTEOARTHRITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABDOMINAL ABSCESS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS BACTERIAL			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABSCESS JAW			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APPENDICITIS PERFORATED			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACTERAEMIA			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHOPNEUMONIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRONCHITIS			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CAMPYLOBACTER GASTROENTERITIS			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CANDIDIASIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
subjects affected / exposed	3 / 525 (0.57%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLOSTRIDIUM DIFFICILE COLITIS			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			

subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA INFECTIOUS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS INFECTIOUS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ERYSIPELAS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA SEPSIS			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GROIN ABSCESS			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HERPES ZOSTER			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HORDEOLUM			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
INCISION SITE CELLULITIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIOUS PERITONITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTIVE TENOSYNOVITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUNG INFECTION			

subjects affected / exposed	4 / 525 (0.76%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
LYMPHANGITIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROTISING FASCIITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC INFECTION			
subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIC SEPSIS			
subjects affected / exposed	15 / 525 (2.86%)	6 / 521 (1.15%)	
occurrences causally related to treatment / all	15 / 15	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL INFECTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCYSTIS JIROVECI PNEUMONIA			

subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	24 / 525 (4.57%)	8 / 521 (1.54%)	
occurrences causally related to treatment / all	19 / 25	4 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
PNEUMONIA BACTERIAL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA INFLUENZAL			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA LEGIONELLA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAL BACTERAEMIA			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMONAL SEPSIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL ABSCESS			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY SYNCYTIAL VIRUS INFECTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	3 / 525 (0.57%)	9 / 521 (1.73%)	
occurrences causally related to treatment / all	2 / 3	4 / 12	
deaths causally related to treatment / all	0 / 0	1 / 3	
SEPTIC SHOCK			
subjects affected / exposed	3 / 525 (0.57%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	2 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
SINUSITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SKIN INFECTION			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL INFECTION			

subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONSILLITIS			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URETHRITIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	10 / 525 (1.90%)	7 / 521 (1.34%)	
occurrences causally related to treatment / all	4 / 10	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION BACTERIAL			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION ENTEROCOCCAL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION FUNGAL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			

subjects affected / exposed	2 / 525 (0.38%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VESTIBULAR NEURONITIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL INFECTION			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	13 / 525 (2.48%)	4 / 521 (0.77%)	
occurrences causally related to treatment / all	10 / 15	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETES MELLITUS INADEQUATE CONTROL			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIABETIC KETOACIDOSIS			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GOUT			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 525 (0.38%)	2 / 521 (0.38%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	3 / 525 (0.57%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	0 / 525 (0.00%)	3 / 521 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 525 (0.19%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	2 / 525 (0.38%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 525 (0.00%)	1 / 521 (0.19%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOVOLAEMIA			
subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METABOLIC ACIDOSIS			

subjects affected / exposed	1 / 525 (0.19%)	0 / 521 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DPL: Docetaxel/ Prednisone/Lenalidomide	DP: Docetaxel/ Prednisone/ Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	513 / 525 (97.71%)	511 / 521 (98.08%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	16 / 525 (3.05%)	33 / 521 (6.33%)	
occurrences (all)	16	43	
HYPOTENSION			
subjects affected / exposed	35 / 525 (6.67%)	24 / 521 (4.61%)	
occurrences (all)	42	33	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	124 / 525 (23.62%)	117 / 521 (22.46%)	
occurrences (all)	263	313	
FATIGUE			
subjects affected / exposed	238 / 525 (45.33%)	232 / 521 (44.53%)	
occurrences (all)	477	472	
MUCOSAL INFLAMMATION			
subjects affected / exposed	37 / 525 (7.05%)	43 / 521 (8.25%)	
occurrences (all)	53	64	
OEDEMA PERIPHERAL			
subjects affected / exposed	146 / 525 (27.81%)	134 / 521 (25.72%)	
occurrences (all)	201	188	
PYREXIA			
subjects affected / exposed	92 / 525 (17.52%)	74 / 521 (14.20%)	
occurrences (all)	142	109	
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	108 / 525 (20.57%)	76 / 521 (14.59%)	
occurrences (all)	139	106	
DYSPNOEA			
subjects affected / exposed	104 / 525 (19.81%)	88 / 521 (16.89%)	
occurrences (all)	145	120	
EPISTAXIS			
subjects affected / exposed	37 / 525 (7.05%)	52 / 521 (9.98%)	
occurrences (all)	46	77	
OROPHARYNGEAL PAIN			
subjects affected / exposed	30 / 525 (5.71%)	20 / 521 (3.84%)	
occurrences (all)	32	25	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	60 / 525 (11.43%)	64 / 521 (12.28%)	
occurrences (all)	67	69	
Investigations			
WEIGHT DECREASED			
subjects affected / exposed	96 / 525 (18.29%)	54 / 521 (10.36%)	
occurrences (all)	131	66	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	61 / 525 (11.62%)	48 / 521 (9.21%)	
occurrences (all)	80	66	
DYSGEUSIA			
subjects affected / exposed	113 / 525 (21.52%)	124 / 521 (23.80%)	
occurrences (all)	154	194	
HEADACHE			
subjects affected / exposed	42 / 525 (8.00%)	51 / 521 (9.79%)	
occurrences (all)	63	71	
PARAESTHESIA			
subjects affected / exposed	34 / 525 (6.48%)	65 / 521 (12.48%)	
occurrences (all)	44	81	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	99 / 525 (18.86%)	130 / 521 (24.95%)	
occurrences (all)	134	225	
Blood and lymphatic system disorders			

ANAEMIA			
subjects affected / exposed	154 / 525 (29.33%)	94 / 521 (18.04%)	
occurrences (all)	323	138	
LEUKOPENIA			
subjects affected / exposed	40 / 525 (7.62%)	34 / 521 (6.53%)	
occurrences (all)	94	51	
NEUTROPENIA			
subjects affected / exposed	125 / 525 (23.81%)	94 / 521 (18.04%)	
occurrences (all)	252	201	
THROMBOCYTOPENIA			
subjects affected / exposed	39 / 525 (7.43%)	18 / 521 (3.45%)	
occurrences (all)	81	27	
Eye disorders			
LACRIMATION INCREASED			
subjects affected / exposed	53 / 525 (10.10%)	63 / 521 (12.09%)	
occurrences (all)	61	79	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	55 / 525 (10.48%)	36 / 521 (6.91%)	
occurrences (all)	69	50	
CONSTIPATION			
subjects affected / exposed	144 / 525 (27.43%)	124 / 521 (23.80%)	
occurrences (all)	198	156	
DIARRHOEA			
subjects affected / exposed	236 / 525 (44.95%)	204 / 521 (39.16%)	
occurrences (all)	452	357	
DYSPEPSIA			
subjects affected / exposed	41 / 525 (7.81%)	30 / 521 (5.76%)	
occurrences (all)	45	36	
NAUSEA			
subjects affected / exposed	170 / 525 (32.38%)	153 / 521 (29.37%)	
occurrences (all)	237	268	
STOMATITIS			
subjects affected / exposed	50 / 525 (9.52%)	37 / 521 (7.10%)	
occurrences (all)	67	55	
VOMITING			

subjects affected / exposed	93 / 525 (17.71%)	63 / 521 (12.09%)	
occurrences (all)	128	86	
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	223 / 525 (42.48%)	226 / 521 (43.38%)	
occurrences (all)	255	262	
DRY SKIN			
subjects affected / exposed	39 / 525 (7.43%)	50 / 521 (9.60%)	
occurrences (all)	43	55	
NAIL DISCOLOURATION			
subjects affected / exposed	22 / 525 (4.19%)	32 / 521 (6.14%)	
occurrences (all)	22	37	
NAIL DISORDER			
subjects affected / exposed	41 / 525 (7.81%)	59 / 521 (11.32%)	
occurrences (all)	49	69	
ONYCHOMADESIS			
subjects affected / exposed	14 / 525 (2.67%)	28 / 521 (5.37%)	
occurrences (all)	17	36	
PRURITUS			
subjects affected / exposed	46 / 525 (8.76%)	10 / 521 (1.92%)	
occurrences (all)	52	15	
RASH			
subjects affected / exposed	61 / 525 (11.62%)	59 / 521 (11.32%)	
occurrences (all)	100	83	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	86 / 525 (16.38%)	73 / 521 (14.01%)	
occurrences (all)	135	104	
BACK PAIN			
subjects affected / exposed	88 / 525 (16.76%)	91 / 521 (17.47%)	
occurrences (all)	118	118	
BONE PAIN			
subjects affected / exposed	59 / 525 (11.24%)	66 / 521 (12.67%)	
occurrences (all)	85	91	
MUSCLE SPASMS			

subjects affected / exposed	85 / 525 (16.19%)	46 / 521 (8.83%)	
occurrences (all)	137	55	
MUSCULAR WEAKNESS			
subjects affected / exposed	25 / 525 (4.76%)	30 / 521 (5.76%)	
occurrences (all)	33	43	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	31 / 525 (5.90%)	27 / 521 (5.18%)	
occurrences (all)	35	33	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	39 / 525 (7.43%)	29 / 521 (5.57%)	
occurrences (all)	46	39	
MYALGIA			
subjects affected / exposed	44 / 525 (8.38%)	55 / 521 (10.56%)	
occurrences (all)	64	69	
PAIN IN EXTREMITY			
subjects affected / exposed	57 / 525 (10.86%)	66 / 521 (12.67%)	
occurrences (all)	75	84	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	46 / 525 (8.76%)	37 / 521 (7.10%)	
occurrences (all)	57	48	
URINARY TRACT INFECTION			
subjects affected / exposed	36 / 525 (6.86%)	32 / 521 (6.14%)	
occurrences (all)	51	48	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	125 / 525 (23.81%)	105 / 521 (20.15%)	
occurrences (all)	173	150	
DEHYDRATION			
subjects affected / exposed	38 / 525 (7.24%)	23 / 521 (4.41%)	
occurrences (all)	54	38	
HYPERGLYCAEMIA			
subjects affected / exposed	35 / 525 (6.67%)	36 / 521 (6.91%)	
occurrences (all)	50	63	
HYPOKALAEMIA			

subjects affected / exposed occurrences (all)	63 / 525 (12.00%) 87	22 / 521 (4.22%) 31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2010	1. Exclusion Criteria #9 was modified to allow subjects exhibiting clinical symptoms or who had rapidly progressive disease to initiate treatment if in the clinical judgment of the investigator a 4- or 6-week delay for an antiandrogen washout period would have compromised the health and safety of the subject. 2. The Schedule of Assessments was modified to provide clarification that a 14-day safety assessment was to be performed for all study subjects unless a review of the safety data by an independent DMC recommended that this safety assessment was no longer necessary. 3. The section defining lenalidomide dose modifications and interruptions was revised to allow subjects to restart lenalidomide if lenalidomide was interrupted during a treatment cycle for toxicity and to remove language requiring subjects to be discontinued from lenalidomide treatment if this treatment was held or interrupted during any part of 2 consecutive cycles 4. Language was added to clarify the definition regarding the use of central and local labs in this study.
09 June 2011	1. Added requirement that SPMs be treated as SAEs and reported throughout the study duration up to 5 years following discontinuation of study drug or until all subjects have expired. 2. Allowed the administration of Myeloid Growth Factors as primary prophylaxis for subjects initiating study treatment, and strongly recommended prophylaxis for subjects with a high risk of developing febrile neutropenia as defined by American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines.
19 January 2012	This amendment was issued following the decision to discontinue treatment with lenalidomide/placebo due to futility. The objectives of Amendment 3 were as follows: 1. To continue to collect information on SPMs and additional treatments for prostate cancer in all randomized subjects during survival follow-up. The change reflects a company-wide decision to revise the collection of SPMs from 5 years following the discontinuation of study drug to 5 years following the last subject randomized. 2. To continue to provide docetaxel and prednisone to CRPC subjects randomized at non-US sites who were ongoing in the CC-5013-PC-002 (Amendment 2, Version dated 09 Jun 2011) protocol when the decision was made to discontinue lenalidomide/placebo and are experiencing benefit as per investigator discretion. Key changes of Amendment 3 were as follows: 1. Removal of all references to dosing and study procedures pertaining to the safety, efficacy, and exploratory endpoints of lenalidomide/placebo. 2. Subjects outside the USA who were ongoing when the decision was made to discontinue lenalidomide/placebo treatment and who were experiencing benefit as per investigator's discretion, were allowed to continue to receive docetaxel/prednisone, up to 10 cycles. For subjects who have been treated beyond 10 cycles, an additional 2 cycles were to be provided. 3. Efficacy was no longer assessed. 4. Second primary malignancies will be reported as SAEs for up to 5 years from the date of randomization of the last subject.

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.

The independent DMC concluded that it was unlikely the trial would achieve its primary endpoint of improved overall survival. The sponsor agreed and the experimental lenalidomide/placebo treatment arm of the study was discontinued.

Notes: