Clinical trial results:
A Randomized, Double-Blind, Phase 3 Trial Comparing Ipilimumab vs. Placebo
Following Radiotherapy in Subjects with Castration Resistant Prostate Cancer That Have Received Prior Treatment with Docetaxel.

Summary

EudraCT number	2008-003314-97
Trial protocol	DE AT NL IT CZ DK ES IE BE GB HU FR GR
Global end of trial date	03 June 2015

Results information

Result version number	v1 (current)
This version publication date	20 August 2016
First version publication date	20 August 2016

Trial information

Trial identification

Sponsor protocol code	CA184-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00861614
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	03 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare OS of subjects with castration resistant prostate cancer (CRPC), that had progressed during or following docetaxel treatment, when randomized to treatment with bone-directed radiotherapy followed by ipilimumab versus bone-directed radiotherapy followed by placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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	Romania: 24
Country: Number of subjects enrolled	Netherlands: 42
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 42
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Denmark: 46
Country: Number of subjects enrolled	France: 77
Country: Number of subjects enrolled	Germany: 30
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 52
Country: Number of subjects enrolled	Argentina: 73
Country: Number of subjects enrolled	Australia: 33

Country: Number of subjects enrolled	Brazil: 79
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 32
Country: Number of subjects enrolled	Colombia: 7
Country: Number of subjects enrolled	Israel: 10
Country: Number of subjects enrolled	Mexico: 46
Country: Number of subjects enrolled	Peru: 19
Country: Number of subjects enrolled	Puerto Rico: 4
Country: Number of subjects enrolled	Russian Federation: 29
Country: Number of subjects enrolled	United States: 215
Worldwide total number of subjects	988
EEA total number of subjects	434

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)	327
From 65 to 84 years	655
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 153 sites in 27 countries.

Pre-assignment

Screening details:

988 enrolled, 799 randomized (399 ipilimumab, 400 placebo); 149 no longer met study criteria, 17 withdrew, 6 adverse events, 4 died, 1 lost to follow-up, 12 unspecified. 789 treated with radiotherapy (393 ipilimumab, 396 placebo); 2 no longer met study criteria, 3 withdrew consent, 1 died, 2 had adverse events, 2 had disease progression.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ipilimumab + Radiotherapy

Arm description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	BMS-734016
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Arm title	Placebo + Radiotherapy

Arm description:

Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Arm type	Placebo

Investigational medicinal product name	Sodium Chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Investigational medicinal product name	Dextrose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Number of subjects in period 1[1]	Ipilimumab + Radiotherapy	Placebo + Radiotherapy
Started	399	400
Completed	22	28
Not completed	377	372
Adverse event, serious fatal	32	19
Consent withdrawn by subject	35	37
Adverse event, non-fatal	27	23
Unspecified	21	23
Study Drug Toxicity	79	6
Disease Progression	183	264

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 988 enrolled, 799 randomized (399 ipilimumab, 400 placebo); 149 no longer met study criteria, 17 withdrew, 6 adverse events, 4 died, 1 lost to follow-up,12 unspecified. 789 treated with radiotherapy (393 ipilimumab, 396 placebo); 2 no longer met study criteria, 3 withdrew consent, 1 died, 2 had adverse events, 2 had disease progression.

Baseline characteristics

Reporting groups	
Reporting group title	Ipilimumab + Radiotherapy
Reporting group description:	
Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.	
Reporting group title	Placebo + Radiotherapy
Reporting group description:	
Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.	

Reporting group values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy	Total
Number of subjects	399	400	799
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
<70 years	215	234	449
>=70 years	184	166	350
Age Continuous Units: years			
arithmetic mean	68.2	67.1	
standard deviation	± 7.53	± 7.56	-
Gender, Male/Female Units: subjects			
Female	0	0	0
Male	399	400	799

End points reporting groups

Reporting group title	Ipilimumab + Radiotherapy
Reporting group description:	
Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.	
Reporting group title	Placebo + Radiotherapy
Reporting group description:	
Subjects receive radiotherapy at 8 Gy to at least 1, and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.	
Subject analysis set title	All Randomized Subjects Ipilimumab + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab.	
Subject analysis set title	All Randomized Subjects in Placebo + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo.	
Subject analysis set title	Pain-Evaluable Subjects in Ipilimumab + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab with a baseline average daily worst pain score of 4 or higher for a 5 day period.	
Subject analysis set title	Pain-Evaluable Subjects in Placebo + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo with a baseline average daily worst pain score of 4 or higher for a 5 day period.	
Subject analysis set title	Subjects with Pain Response in Ipilimumab + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of ipilimumab with a baseline average daily worst pain score of 4 or higher for a 5 day period.	
Subject analysis set title	Subjects with pain response in Placebo + Radiotherapy Arm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All subjects who received pretreatment bone-directed radiotherapy and at least 1 dose of placebo with a baseline average daily worst pain score of 4 or higher for a 5 day period.	

Primary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
OS was defined as the time in months from randomization date to date of death due to any cause in all randomized subjects. For subjects alive at the time of the database cutoff date, OS was censored at the last date the subject was known to be alive. The analysis population included all randomized subjects defined as all enrolled subjects that were randomized.	

End point type	Primary

End point timeframe:

Date of randomization to date of death, approximately 5 years

End point values	All Randomized Subjects Ipilimumab + Radiotherapy Arm	All Randomized Subjects in Placebo + Radiotherapy Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	399	400		
Units: months				
median (confidence interval 95%)	11.04 (9.46 to 12.48)	10.02 (8.38 to 11.17)		

Statistical analyses

Statistical analysis title	Overall Survival Comparison
Comparison groups	All Randomized Subjects Ipilimumab + Radiotherapy Arm v All Randomized Subjects in Placebo + Radiotherapy Arm
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0127
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.96

Primary: Overall Survival Rate

End point title	Overall Survival Rate[1]

End point description:

The overall survival (OS) rate was a percentage, representing the fraction of all randomized subjects who were alive following one year of treatment. OS was defined as the time between the date of randomization and the date of death as a result of any cause. Survival rates were determined via Kaplan-Meier estimates. The analysis population included all randomized subjects.

End point type	Primary

End point timeframe:

Date of randomization to date of death, approximately 5 years

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive summary statistics were planned for this outcome measure.

End point values	All Randomized Subjects Ipilimumab + Radiotherapy Arm	All Randomized Subjects in Placebo + Radiotherapy Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	399	400		
Units: percentage of subjects				
number (confidence interval 95%)				
OS Rate at Year 1	46.5 (41.6 to 51.4)	40.8 (35.9 to 45.6)		
OS Rate at Year 2	25.2 (20.9 to 29.6)	16.6 (12.9 to 20.3)		
OS Rate at Year 3	15.3 (15.3 to 18.9)	7.9 (5.2 to 10.6)		
OS Rate at Year 4	10.1 (6.9 to 13.3)	3.3 (1.3 to 5.3)		
OS Rate at Year 5	7.9 (4.4 to 11.4)	2.7 (0.8 to 4.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

All PFS events were based on investigator’s assessment. Subjects who were alive and did not experience a PFS event were censored at the earlier of the latest prostate-specific antigen (PSA) or radiological tumor assessment date. Subjects who did not die, showed no clinical deterioration, and who had no recorded post-baseline PSA or radiological tumor assessment were censored at randomization date. The analysis population included all randomized subjects.

End point type	Secondary

End point timeframe:

Date of randomization to earliest date of confirmed PSA or radiological progression, clinical deterioration or death, up to November 2012, approximately 3.5 years

End point values	All Randomized Subjects Ipilimumab + Radiotherapy Arm	All Randomized Subjects in Placebo + Radiotherapy Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	399	400		
Units: months				
median (confidence interval 95%)	4.01 (3.65 to 4.34)	3.06 (2.86 to 3.42)		

Statistical analyses

Statistical analysis title	Progression Free Survival Comparison
Comparison groups	All Randomized Subjects Ipilimumab + Radiotherapy Arm v All Randomized Subjects in Placebo + Radiotherapy Arm
Number of subjects included in analysis	799
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	0.82

Secondary: Pain Response

End point title	Pain Response

End point description:

The percentage of subjects with a pain response assessed using the Brief Pain Inventory Short Form (BPI-SF) completed by subjects throughout the study in a daily diary log. Pain-evaluable subjects were defined as those with a decrease in the average daily worst pain intensity by at least 30% from baseline, maintained over 2 consecutive evaluations without the use of any rescue analgesic medication or increase in analgesic use in the same time period. The analysis population included all pain-evaluable subjects.

End point type	Secondary

End point timeframe:

Assessed at screening, weeks 12, 18, 24, and at the end of treatment visit

End point values	Pain-Evaluable Subjects in Ipilimumab + Radiotherapy Arm	Pain-Evaluable Subjects in Placebo + Radiotherapy Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	197	186		
Units: percentage of subjects				
number (confidence interval 95%)	3.55 (1.44 to 7.18)	0.54 (0.01 to 2.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Pain Response

End point title	Duration of Pain Response

End point description:

The time between the initial date of pain response and completion date of pain response. The initial date when the pain response criterion was achieved was considered the pain response date. The earlier of

date of death, date of tumor resection surgery, or date when pain response criterion was no longer met was considered the completion date of the pain response. If none of these scenarios occurred, the completion of the pain response was set to the last known alive date. The analysis population included all pain-evaluable subjects with a pain response. Here -99999 to 99999 signifies that no confidence interval is applicable due to only one subject being analyzed.

End point type	Secondary

End point timeframe:

Day of initial pain response to day of completion of pain response or date of death

End point values	Subjects with Pain Response in Ipilimumab + Radiotherapy Arm	Subjects with pain response in Placebo + Radiotherapy Arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	1		
Units: months				
median (confidence interval 95%)	2.5 (1.5 to 3)	1.5 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	Duration of Pain Response Comparison
Comparison groups	Subjects with pain response in Placebo + Radiotherapy Arm v Subjects with Pain Response in Ipilimumab + Radiotherapy Arm
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	4

Secondary: Number of Subjects With Severe Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Related AEs, Deaths, Discontinuation of Study Drug Due to AEs, Immune-Related Adverse Events (irAE) and Immune-Mediated Adverse Reaction (imAR)

End point title	Number of Subjects With Severe Adverse Events (AEs), Serious Adverse Events (SAEs), Treatment-Related AEs, Deaths, Discontinuation of Study Drug Due to AEs, Immune-Related Adverse Events (irAE) and Immune-Mediated Adverse Reaction (imAR)

End point description:

AE=new unfavorable symptom, sign, disease or worsening preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or

significant disability/incapacity or drug dependency/abuse; is life-threatening, an important medical event or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Treatment-related=having certain, possible or missing relationship to study drug. Death=during study and up to 70 days after last dose. IrAEs=AEs potentially associated with inflammation, considered to be causally related to study drug and grouped into gastrointestinal (GI), hepatic, skin, endocrine and neurological. ImARs were collected prospectively and grouped into enterocolitis, hepatitis, dermatitis, neuropathies and endocrinopathies. Grading used Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Ver.3.0. The analysis population included all treated subjects

End point type	Secondary

End point timeframe:

Randomization to date of death, up to approximately 5 years

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: subjects				
number (not applicable)				
SAE	257	164		
Treatment-Related AE	296	180		
Any Death	346	371		
Deaths Due to Study Drug Toxicity	7	1		
Discontinuation of Study Drug due to AEs	137	62		
Immune-Related AE (any grade)	250	86		
Immune-Mediated Adverse Reaction (Grade >=2)	203	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Grade 3 or 4 Immune-Related Adverse Event (irAE)

End point title	Time to Onset of Grade 3 or 4 Immune-Related Adverse Event (irAE)

End point description:

The time between first dose of study drug and date of earliest Grade 3 or 4 irAE. These irAEs are AEs of unknown etiology, consistent with an immune phenomenon and considered as causally related to drug exposure. The five subcategories of irAE examined include gastrointestinal (GI), liver, skin, endocrine, and neurological and are graded using the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0. The analysis population included all treated subjects assessed for onset of adverse events. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

End point type	Secondary

End point timeframe:

Day 1 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: weeks				
median (confidence interval 95%)				
Gastrotintestinal (n= 71,3)	5.71 (5 to 7)	5.71 (0.57 to 31.86)		
Liver (n= 18,5)	9.14 (8.29 to 10.43)	6 (3.14 to 8.57)		
Skin (n=4,0)	3.71 (2.57 to 6.43)	99999 (-99999 to 99999)		
Endocrine (n=8,2)	7.93 (4.14 to 11.14)	5 (4.29 to 5.71)		
Neurological (n= 1,0)	11.4 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Grade 3 or 4 Immune-Related Adverse Event (irAE)

End point title	Time to Resolution of Grade 3 or 4 Immune-Related Adverse Event (irAE)

End point description:

Time between the date of onset of a Grade 3 or 4 irAE and the date of improvement to Grade 1 or less or the worst grade at baseline. The analysis population included all treated subjects assessed for onset of adverse events. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

End point type	Secondary

End point timeframe:

Day 1 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: weeks				
median (confidence interval 95%)				
Gastrointestinal (n=71,3)	2.9 (1.6 to 4.7)	0.9 (0.4 to 1.1)		
Liver (n=18,5)	4.1 (3.6 to 8.1)	6 (1.9 to 99999)		
Skin (n=4,0)	3.6 (2.6 to 5.9)	99999 (-99999 to 99999)		
Endocrine (n=8,2)	11.1 (2.4 to 99999)	5.9 (0.9 to 10.9)		
Neurological (n=1,0)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Grade 3 to 5 Immune-Mediated Adverse Reaction (imAR)

End point title	Time to Onset of Grade 3 to 5 Immune-Mediated Adverse Reaction (imAR)[2]

End point description:

The time between first dose of study drug and date of earliest Grade 3 or 4 imAR. ImARs were collected prospectively and grouped into enterocolitis, hepatitis, dermatitis, neuropathies and endocrinopathies and graded using Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events (CTCAE), Ver. 3.0.
Only the Ipilimumab + Radiotherapy group of subjectss was included in the analysis because ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity likely to be related to its mechanism of action. The analysis population included all treated subjects in the Ipilimumab + radiology arm.

End point type	Secondary

End point timeframe:

Day 1 to time of onset of the imAR of interest

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arm receiving study drug was analyzed for this endpoint. Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity.

End point values	Ipilimumab + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	393			
Units: weeks				
median (full range (min-max))				
Enterocolitis (n=65)	3.4 (0.3 to 16.6)			
Hepatitis (n=17)	9 (1.7 to 16.9)			
Dermatitis (n=3)	2.4 (0.1 to 3.1)			
Endocrinopathies (n=6)	7.9 (1.7 to 10.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Resolution of Grade 3 to 5 to Grade 0 Immune-Mediated Adverse Reactions (imARs) to Grade 0

End point title	Time to Resolution of Grade 3 to 5 to Grade 0 Immune-Mediated Adverse Reactions (imARs) to Grade 0[3]

End point description:

Time between the date of onset of an imAR to the date of resolution date of the event or the last known date subject was alive if an event did not resolve.
Only the Ipilimumab + Radiotherapy group of subjects was included in the analysis because ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity likely to be related to its mechanism of action. The analysis population included all treated subjects in the Ipilimumab + radiotherapy arm. Here 99999 signifies that there were no subjects in this treatment arm who displayed irAEs of this type and -99999 to 99999 signifies that no confidence interval was applicable due to only one subject being analyzed.

End point type	Secondary

End point timeframe:

Day 1 to 70 days after last dose of study drug

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only the arm receiving study drug was analyzed for this endpoint. Ipilimumab is associated with inflammatory events resulting from increased or excessive immune activity.

End point values	Ipilimumab + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	393			
Units: weeks				
median (full range (min-max))				
Enterocolitis (n=52)	6 (0.1 to 40.1)			
Hepatitis (n=15)	8.6 (1.1 to 19)			
Dermatitis (n=3)	6.9 (4 to 12.1)			
Endocrinopathies (n=0)	99999 (-99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Hematology Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point title	Number of Subjects with Worst On-Study Hematology Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point description:

Comparison of baseline versus worst grade hematology laboratory tests as measured by white blood count (WBC), absolute neutrophil count (ANC), platelet count, hemoglobin and lymphocyte results. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0: within normal range. Abnormal values for WBC were based on Gr 1: 3.0 - < Lower Limit of Normal (LLN); Gr 2: 2.0 - < 3.0; Gr 3: 1.0 - < 2.0; Gr4: < 1.0. Abnormal values for Hemoglobin were based on Gr 1: 10.0 - < LLN; Gr 2: 8.0 - < 10.0; Gr 3: 6.5 - < 8.0; Gr 4: < 6.5. Abnormal values for Lymphocytes were based on Gr 1: 0.8 - < 1.5; Gr 2: 0.5 - < 0.8; Gr 3): 0.2 - < 0.5; Gr 4: < 0.2. Abnormal values for ANC were based on Gr 1: 1.5 - < 2.0; Gr 2: 1.0 - < 1.5; Gr 3: 0.5 - < 1.0; Gr 4: < 0.5. Abnormal values for Platelets were based on Gr 1: 75.0 - < LLN; Gr 2: 50.0 - < 75.0; Gr 3: 25.0 - < 50.0; Gr 4: < 25.0. Analysis population included all treated subjects.

End point type	Secondary

End point timeframe:

Day 2 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: subjects				
number (not applicable)				
WBC Gr 0 at Baseline to Gr 3-4	3	2		
WBC Gr 1 at Baseline to Gr 3-4	0	1		
WBC Gr 2 at Baseline to Gr 3-4	0	1		
WBC Gr 3 at Baseline to Gr 3-4	0	0		
WBC Gr 4 at Baseline to Gr 3-4	0	0		
WBC Not Reported at Baseline to Gr 3-4	0	0		
ANC Gr 0 at Baseline to Gr 3-4	4	6		
ANC Gr 1 at Baseline to Gr 3-4	0	0		
ANC Gr 2 at Baseline to Gr 3-4	0	0		
ANC Gr 3 at Baseline to Gr 3-4	0	0		
ANC Gr 4 at Baseline to Gr 3-4	0	0		
ANC Not Reported at Baseline to Gr 3-4	1	0		
Platelet Count Gr 0 at Baseline to Gr 3-4	1	6		
Platelet Count Gr 1 at Baseline to Gr 3-4	1	1		
Platelet Count Gr 2 at Baseline to Gr 3-4	0	0		
Platelet Count Gr 3 at Baseline to Gr 3-4	0	0		
Platelet Count Gr 4 at Baseline to Gr 3-4	0	0		
Platelet Count Not Reported at Baseline to Gr 3-4	1	1		
Hemoglobin Gr 0 at Baseline to Gr 3-4	0	3		
Hemoglobin Gr 1 at Baseline to Gr 3-4	16	25		
Hemoglobin Gr 2 at Baseline to Gr 3-4	13	11		
Hemoglobin Gr 3 at Baseline to Gr 3-4	0	1		
Hemoglobin Gr 4 at Baseline to Gr 3-4	0	0		
Hemoglobin Not Reported at Baseline to Gr 3-4	0	1		
Lymphocytes Gr 0 at Baseline to Gr 3-4	4	1		
Lymphocytes Gr 1 at Baseline to Gr 3-4	6	11		
Lymphocytes Gr 2 at Baseline to Gr 3-4	11	17		
Lymphocytes Gr 3 at Baseline to Gr 3-4	8	7		
Lymphocytes Gr 4 at Baseline to Gr 3-4	0	0		
Lymphocytes Not Reported at Baseline to Gr 3-4	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Liver Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point title	Number of Subjects with Worst On-Study Liver Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point description:

Comparison of baseline versus worst grade liver function as measured by alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin and alkaline phosphatase (ALP). National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0:

within normal range. Abnormal values for ALP, ALT and AST were based on grades; Gr 1: > 1.0 - 2.5 * upper limits of normal (ULN); Gr 2: > 2.5 - 5.0 * ULN; Gr 3: > 5.0 - 20.0 * ULN; Gr 4: > 20.0 * ULN. Abnormal values for Total Bilirubin were based on Gr 1: > 1.0 - 1.5 * upper limits of normal (ULN); Gr 2: > 1.5 - 3.0 * ULN; Gr 3: > 3.0 - 10.0 * ULN; Gr 4: > 10.0 * ULN. Analysis population included all treated subjects.

End point type	Secondary

End point timeframe:

Day 2 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: subjects				
number (not applicable)				
ALT Gr 0 at Baseline to Gr 3-4	16	1		
ALT Gr 1 at Baseline to Gr 3-4	1	1		
ALT Gr 2 at Baseline to Gr 3-4	0	0		
ALT Gr 3 at Baseline to Gr 3-4	0	0		
ALT Gr 4 at Baseline to Gr 3-4	0	0		
ALT Not reported at Basline to Gr 3-4	1	0		
AST Gr 0 at Baseline to Gr 3-4	15	6		
AST Gr 1 at Baseline to Gr 3-4	5	1		
AST Gr 2 at Baseline to Gr 3-4	1	1		
AST Gr 3 at Baseline to Gr 3-4	1	0		
AST Gr 4 at Baseline to Gr 3-4	0	0		
AST Not Reported at Baseline to Gr 3-4	1	0		
Total Bilirubin Gr 0 at Baseline to Gr 3-4	6	2		
Total Bilirubin Gr 1 at Baseline to Gr 3-4	1	0		
Total Bilirubin Gr 2 at Baseline to Gr 3-4	1	0		
Total Bilirubin Gr 3 at Baseline to Gr 3-4	0	0		
Total Bilirubin Gr 4 at Baseline to Gr 3-4	0	0		
Total Bilirubin Not Reported at Baseline to Gr 3-4	0	0		
ALP Gr 0 at Baseline to Gr 3-4	1	1		
ALP Gr 1 at Baseline to Gr 3-4	10	17		
ALP Gr 2 at Baseline to Gr 3-4	21	29		
ALP Gr 3 at Baseline to Gr 3-4	27	42		
ALP Gr 4 at Baseline to Gr 3-4	1	0		
ALP Not Reported at Baseline to Gr 3-4	0	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Serum Chemistry Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point title	Number of Subjects with Worst On-Study Serum Chemistry Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point description:

Comparison of baseline versus worst grade serum chemistry as measured by lipase and amylase analysis. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr). Gr 0: within normal range. Abnormal values for lipase: Gr1: > 1.0 - 1.5 * ULN; Gr2: > 1.5 - 2.0 * ULN; Gr 3: > 2.0 - 5.0 * ULN; Gr4: > 5.0*ULN. Abnormal values for amylase: Gr1: > 1.0 - 1.5 * ULN; Gr 2: > 1.5 - 2.0 * ULN; Gr 3: > 2.0 - 5.0 * ULN; Gr4: > 5.0 * ULN. Analysis population included all treated subjects.

End point type	Secondary

End point timeframe:

Day 2 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: subjects				
number (not applicable)				
Lipase Gr 0 at Baseline to Gr 3-4	21	10		
Lipase Gr 1 at Baseline to Gr 3-4	1	1		
Lipase Gr 2 at Baseline to Gr 3-4	1	0		
Lipase Gr 3 at Baseline to Gr 3-4	0	1		
Lipase Gr 4 at Baseline to Gr 3-4	0	0		
Lipase Not reported at Basline to Gr 3-4	0	0		
Amylase Gr 0 at Baseline to Gr 3-4	4	4		
Amylase Gr 1 at Baseline to Gr 3-4	1	1		
Amylase Gr 2 at Baseline to Gr 3-4	3	1		
Amylase Gr 3 at Baseline to Gr 3-4	1	0		
Amylase Gr 4 at Baseline to Gr 3-4	0	0		
Amylase Not Reported at Baseline to Gr 3-4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Worst On-Study Renal Function Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point title	Number of Subjects with Worst On-Study Renal Function Common Toxicity Criteria (CTC) Grade and Shift from Baseline

End point description:

Comparison of baseline versus worst grade renal function as measured by creatinine analysis. National Cancer Institute Common Terminology Criteria (CTC) version (v) 3.0 was used to determine Grade (Gr).Gr 0: within normal range. Abnormal values for Creatinine were based on Gr 1: > 1.0 - 1.5*ULN; Gr 2: > 1.5 - 3.0*ULN; Gr 3: > 3.0 - 6.0*ULN; Gr 4: > 6.0*ULN. Analysis population included all treated subjects.

End point type	Secondary

End point timeframe:

Day 2 to 70 days after last dose of study drug

End point values	Ipilimumab + Radiotherapy	Placebo + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	393	396		
Units: subjects				
number (not applicable)				
Creatinine Gr 0 at Baseline to Gr 3-4	3	3		
Creatinine Gr 1 at Baseline to Gr 3-4	0	0		
Creatinine Gr 2 at Baseline to Gr 3-4	0	0		
Creatinine Gr 3 at Baseline to Gr 3-4	0	0		
Creatinine Gr 4 at Baseline to Gr 3-4	0	0		
Creatinine Not Reported at Baseline to Gr 3-4	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 to 70 days following the last dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Ipilimumab + Radiotherapy

Reporting group description:

Prior to receiving study drug, subjects receive radiotherapy at 8 Gray units (Gy) to at least 1 and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, 10 milligrams (mg) of ipilimumab per kilogram (kg) of body weight was administered intravenously (IV) over 90 minutes. During the treatment phase, dosing was at weeks 1, 4,7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD), drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Reporting group title	Placebo + Radiotherapy

Reporting group description:

Subjects receive radiotherapy at 8 Gy to at least 1 and up to a maximum of 5, bone fields, all in one day. Within 2 days of radiotherapy, placebo solution (0.9% sodium chloride or 5% dextrose) infused IV over 90 minutes. During the treatment phase, dosing was at weeks 1, 4, 7 and 10. In the maintenance phase, dosing was a 12-week intervals, beginning at week 24. Dosing continued until confirmed progressive disease (PD),
drug intolerance, clinical deterioration, death, withdrawal of consent or subject lost to follow-up.

Serious adverse events	Ipilimumab + Radiotherapy	Placebo + Radiotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	257 / 393 (65.39%)	164 / 396 (41.41%)	
number of deaths (all causes)	81	62	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellopontine angle tumour			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm of spinal cord			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	36 / 393 (9.16%)	31 / 396 (7.83%)	
occurrences causally related to treatment / all	0 / 36	0 / 31	
deaths causally related to treatment / all	0 / 34	0 / 29	
Metastases to bone			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 393 (0.25%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypotension			
subjects affected / exposed	3 / 393 (0.76%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral ischaemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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 / 393 (0.25%)	0 / 396 (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	9 / 393 (2.29%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	6 / 11	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 2	
Chest pain			
subjects affected / exposed	2 / 393 (0.51%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Fatigue			
subjects affected / exposed	13 / 393 (3.31%)	10 / 396 (2.53%)	
occurrences causally related to treatment / all	5 / 16	2 / 10	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical health deterioration			
subjects affected / exposed	16 / 393 (4.07%)	8 / 396 (2.02%)	
occurrences causally related to treatment / all	0 / 16	0 / 9	
deaths causally related to treatment / all	0 / 8	0 / 5	
Malaise			

subjects affected / exposed	7 / 393 (1.78%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	9 / 10	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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	2 / 393 (0.51%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 2	1 / 4	
Oedema peripheral			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	6 / 393 (1.53%)	10 / 396 (2.53%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 4	
Performance status decreased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	17 / 393 (4.33%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	8 / 19	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral swelling			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Autoimmune disorder			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	8 / 393 (2.04%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	1 / 14	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 1	
Epistaxis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoxia			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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	4 / 393 (1.02%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 393 (0.76%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	2 / 2	0 / 2	
Pulmonary hypertension			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	3 / 393 (0.76%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self injurious behaviour			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 393 (1.53%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	4 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	7 / 393 (1.78%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase decreased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	3 / 393 (0.76%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-Reactive protein increased			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eastern cooperative oncology group performance status worsened			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoglobin decreased			
subjects affected / exposed	13 / 393 (3.31%)	7 / 396 (1.77%)	
occurrences causally related to treatment / all	1 / 17	0 / 12	
deaths causally related to treatment / all	0 / 1	0 / 1	

General physical condition abnormal			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	3 / 393 (0.76%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Red blood cell count decreased			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fissure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Arrhythmia			

subjects affected / exposed	3 / 393 (0.76%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory arrest			

subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (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 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brachial plexopathy			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral haematoma			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 393 (0.76%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depressed level of consciousness			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 393 (0.25%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological symptom			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraparesis			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Paraplegia			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paresis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	4 / 393 (1.02%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 393 (0.00%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	4 / 393 (1.02%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Syncope			
subjects affected / exposed	1 / 393 (0.25%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tongue paralysis			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal nerve disorder			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 393 (3.82%)	18 / 396 (4.55%)	
occurrences causally related to treatment / all	0 / 17	1 / 22	
deaths causally related to treatment / all	0 / 2	0 / 2	
Anaemia of malignant disease			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 393 (0.25%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	0 / 1	1 / 7	
deaths causally related to treatment / all	0 / 1	1 / 2	
Eye disorders			

Macular degeneration			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pupils unequal			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	4 / 393 (1.02%)	5 / 396 (1.26%)	
occurrences causally related to treatment / all	3 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	21 / 393 (5.34%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	21 / 22	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	7 / 393 (1.78%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	1 / 7	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diarrhoea			
subjects affected / exposed	59 / 393 (15.01%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	65 / 69	4 / 6	
deaths causally related to treatment / all	2 / 2	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	11 / 393 (2.80%)	8 / 396 (2.02%)	
occurrences causally related to treatment / all	7 / 13	4 / 10	
deaths causally related to treatment / all	0 / 2	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	11 / 393 (2.80%)	10 / 396 (2.53%)	
occurrences causally related to treatment / all	9 / 14	4 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal perforation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic gastritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cholecystitis			

subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	4 / 393 (1.02%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	3 / 393 (0.76%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anuria			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder dilatation			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder obstruction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	2 / 393 (0.51%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	6 / 393 (1.53%)	6 / 396 (1.52%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephrolithiasis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	4 / 393 (1.02%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 393 (0.25%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral obstruction			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	7 / 393 (1.78%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	2 / 7	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 0	
Endocrine disorders			
Adrenal insufficiency			

subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	4 / 393 (1.02%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophysitis			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	3 / 393 (0.76%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenocorticotropic hormone deficiency			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	7 / 393 (1.78%)	8 / 396 (2.02%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			

subjects affected / exposed	4 / 393 (1.02%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	5 / 393 (1.27%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 393 (0.00%)	5 / 396 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	3 / 393 (0.76%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	0 / 393 (0.00%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Cavernous sinus thrombosis			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	1 / 393 (0.25%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cystitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 393 (0.51%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Labyrinthitis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lobar pneumonia			
subjects affected / exposed	1 / 393 (0.25%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	18 / 393 (4.58%)	5 / 396 (1.26%)	
occurrences causally related to treatment / all	0 / 19	0 / 5	
deaths causally related to treatment / all	0 / 11	0 / 3	
Periorbital cellulitis			

subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 393 (0.51%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 393 (1.53%)	3 / 396 (0.76%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 4	0 / 3	
Septic shock			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	12 / 393 (3.05%)	4 / 396 (1.01%)	
occurrences causally related to treatment / all	0 / 13	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Urosepsis			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord infection			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 393 (0.76%)	2 / 396 (0.51%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dehydration			
subjects affected / exposed	18 / 393 (4.58%)	10 / 396 (2.53%)	
occurrences causally related to treatment / all	12 / 23	0 / 11	
deaths causally related to treatment / all	1 / 2	0 / 4	
Failure to thrive			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	3 / 393 (0.76%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hypoglycaemia			

subjects affected / exposed	0 / 393 (0.00%)	1 / 396 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 393 (0.51%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 393 (0.25%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 393 (0.76%)	0 / 396 (0.00%)	
occurrences causally related to treatment / all	1 / 3	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	Ipilimumab + Radiotherapy	Placebo + Radiotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	350 / 393 (89.06%)	333 / 396 (84.09%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	26 / 393 (6.62%)	9 / 396 (2.27%)	
occurrences (all)	31	11	
Aspartate aminotransferase increased			
subjects affected / exposed	31 / 393 (7.89%)	21 / 396 (5.30%)	
occurrences (all)	35	24	
Haemoglobin decreased			
subjects affected / exposed	26 / 393 (6.62%)	20 / 396 (5.05%)	
occurrences (all)	34	27	
Weight decreased			
subjects affected / exposed	91 / 393 (23.16%)	56 / 396 (14.14%)	
occurrences (all)	94	56	

Vascular disorders			
Hypertension			
subjects affected / exposed	20 / 393 (5.09%)	13 / 396 (3.28%)	
occurrences (all)	22	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	22 / 393 (5.60%)	18 / 396 (4.55%)	
occurrences (all)	22	23	
Headache			
subjects affected / exposed	38 / 393 (9.67%)	31 / 396 (7.83%)	
occurrences (all)	48	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	79 / 393 (20.10%)	81 / 396 (20.45%)	
occurrences (all)	105	99	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	80 / 393 (20.36%)	64 / 396 (16.16%)	
occurrences (all)	95	71	
Fatigue			
subjects affected / exposed	144 / 393 (36.64%)	120 / 396 (30.30%)	
occurrences (all)	156	121	
Oedema peripheral			
subjects affected / exposed	46 / 393 (11.70%)	33 / 396 (8.33%)	
occurrences (all)	46	34	
Pain			
subjects affected / exposed	33 / 393 (8.40%)	44 / 396 (11.11%)	
occurrences (all)	39	43	
Pyrexia			
subjects affected / exposed	81 / 393 (20.61%)	50 / 396 (12.63%)	
occurrences (all)	97	77	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 393 (8.40%)	25 / 396 (6.31%)	
occurrences (all)	34	27	
Constipation			

subjects affected / exposed	66 / 393 (16.79%)	82 / 396 (20.71%)	
occurrences (all)	70	97	
Diarrhoea			
subjects affected / exposed	186 / 393 (47.33%)	94 / 396 (23.74%)	
occurrences (all)	281	120	
Nausea			
subjects affected / exposed	126 / 393 (32.06%)	104 / 396 (26.26%)	
occurrences (all)	155	122	
Vomiting			
subjects affected / exposed	107 / 393 (27.23%)	80 / 396 (20.20%)	
occurrences (all)	134	102	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 393 (9.16%)	27 / 396 (6.82%)	
occurrences (all)	36	27	
Dyspnoea			
subjects affected / exposed	47 / 393 (11.96%)	32 / 396 (8.08%)	
occurrences (all)	49	33	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	99 / 393 (25.19%)	22 / 396 (5.56%)	
occurrences (all)	119	23	
Rash			
subjects affected / exposed	81 / 393 (20.61%)	27 / 396 (6.82%)	
occurrences (all)	112	31	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 393 (7.89%)	34 / 396 (8.59%)	
occurrences (all)	31	33	
Depression			
subjects affected / exposed	10 / 393 (2.54%)	20 / 396 (5.05%)	
occurrences (all)	10	22	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	44 / 393 (11.20%)	57 / 396 (14.39%)	
occurrences (all)	45	59	

Back pain			
subjects affected / exposed	56 / 393 (14.25%)	74 / 396 (18.69%)	
occurrences (all)	60	77	
Bone pain			
subjects affected / exposed	31 / 393 (7.89%)	53 / 396 (13.38%)	
occurrences (all)	32	53	
Pain in extremity			
subjects affected / exposed	31 / 393 (7.89%)	41 / 396 (10.35%)	
occurrences (all)	35	46	
Musculoskeletal pain			
subjects affected / exposed	32 / 393 (8.14%)	44 / 396 (11.11%)	
occurrences (all)	30	51	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	24 / 393 (6.11%)	24 / 396 (6.06%)	
occurrences (all)	30	25	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	119 / 393 (30.28%)	97 / 396 (24.49%)	
occurrences (all)	124	99	
Dehydration			
subjects affected / exposed	26 / 393 (6.62%)	15 / 396 (3.79%)	
occurrences (all)	30	18	
Hypokalaemia			
subjects affected / exposed	20 / 393 (5.09%)	10 / 396 (2.53%)	
occurrences (all)	22	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2009	Clarified the following: pretreatment radiotherapy and use of standard-of-care radiotherapy while on study; discontinuation of anti-androgen therapy prior to randomization; weight measurement for dose calculation; exclusion of subjects with brain metastases; retreatment with docetaxel following progression after a prior docetaxel-containing regimen as a separate anti-cancer regimen
27 January 2010	Clarified inclusion/exclusion criteria pertaining to the allowable number of prior regimens and performance status in order to more accurately reflect evolving current clinical practice; Modified requirement for saline flush at end of study drug infusion; Updated Appendix 3 to contain complete patient pain diary and added Appendix 5 (SSQ).
02 September 2010	Removed requirement for disease progression during or within 6 months of receiving docetaxel treatment for metastatic CRPC prior to enrollment; Updated that for eligibility purposes, all docetaxel-containing regimens are counted as a single regimen; AEs were to be reported for 90 days after the last dose of study medication;
17 December 2010	Reinstated requirement that subjects were to have received a prior regimen of docetaxel that contained at least 2 cycles of docetaxel; Reinstated requirement that subjects were to have progressed while receiving, or within 6 months of receiving, a docetaxel-containing regimen, and clarified that subjects that have received additional anti-cancer therapy after docetaxel must also have demonstrated progression on that therapy.
03 July 2012	Removed interim analysis that was planned to occur at 435 events (deaths); Added Extension Phase to study design to allow for continued collection of survival and safety data after the database lock for the primary analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported