



Clinical trial results:

Phase 3b, Randomized, Open-Label Study of Bevacizumab + Temsirolimus Versus Bevacizumab + Interferon-Alfa as First-Line Treatment in Subjects With Advanced Renal Cell Carcinoma.

Summary

EudraCT number	2007-003793-26
Trial protocol	HU ES FR BE PT CZ DE SK NL IT GB
Global end of trial date	27 April 2015

Results information

Result version number	v1 (current)
This version publication date	14 April 2016
First version publication date	14 April 2016

Trial information

Trial identification

Sponsor protocol code	3066K1-3311 (B1771006)
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00631371
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Wyeth Research Division of Wyeth Pharmaceuticals Inc.
Sponsor organisation address	500 Arcola Road,, Collegeville, PA, United States, 19426
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	23 September 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 April 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 a comparison of independently assessed progression free survival (PFS) in participants with clear cell advanced RCC (all risk groups) treated with Bevacizumab + Temsirolimus (experimental arm) Versus Bevacizumab + Interferon-Alfa (control arm).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

Background therapy: -

Evidence for comparator:

Roferon (Solution for injection, subcutaneous use).

Actual start date of recruitment	10 April 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Brazil: 45
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Chile: 44
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Hong Kong: 9
Country: Number of subjects enrolled	Hungary: 34
Country: Number of subjects enrolled	India: 42
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Korea, Republic of: 16
Country: Number of subjects enrolled	Malaysia: 2

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Poland: 122
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Russian Federation: 111
Country: Number of subjects enrolled	Serbia: 36
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Slovakia: 22
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Taiwan: 25
Country: Number of subjects enrolled	Ukraine: 51
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	791
EEA total number of subjects	336

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)	576
From 65 to 84 years	214
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 791 participants were randomized (intent to treat [ITT] population) and 784 participants received at least 1 dose of study treatment (safety population); 7 participants did not receive study drug.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio, stratified by prior nephrectomy status (yes/no) and Memorial Sloan Kettering Cancer Center (MSKCC) risk factors (good/intermediate/poor), and received either the combination treatment of Temsirolimus + Bevacizumab (Temsr+Bev) or Interferon-alfa + Bevacizumab (IFN+Bev).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Bevacizumab+Temsirrolimus

Arm description:

Bevacizumab 10 milligram per kilogram (mg/kg) intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with temsirolimus 25 mg intravenous infusion over at least 30 minutes once a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.

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

Dosage and administration details:

Bevacizumab 10 mg/kg was administered as intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along either with either temsirolimus or interferon-alfa.

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

Dosage and administration details:

Temsirrolimus 25 mg was administered as intravenous infusion over at least 30 minutes once a week..

Arm title	Bevacizumab+ Interferon-Alfa
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Arm description:

Bevacizumab 10 mg/kg intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with interferon-alfa (IFN) 9 million units (MU) subcutaneous injection every 3 times a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.

Arm type	Active comparator
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Investigational medicinal product name	Interferon Alfa-2A
Investigational medicinal product code	
Other name	Roferon
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Interferon-alfa (IFN) 9 million units (MU) was administered as subcutaneous injection every 3 times a week.

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

Dosage and administration details:

Bevacizumab 10 mg/kg intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along either with either temsirolimus or interferon-alfa.

Number of subjects in period 1	Bevacizumab+Tems rolimus	Bevacizumab+ Interferon-Alfa
Started	400	391
Treated	393	391
Completed	0	0
Not completed	400	391
Discontinuation of study by Sponsor	70	76
Deaths	263	239
Other reason	5	12
Subject request	38	45
Lost to follow-up	24	19

Baseline characteristics

Reporting groups

Reporting group title	Bevacizumab+Temsirrolimus
Reporting group description: Bevacizumab 10 milligram per kilogram (mg/kg) intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with temsirolimus 25 mg intravenous infusion over at least 30 minutes once a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.	
Reporting group title	Bevacizumab+ Interferon-Alfa
Reporting group description: Bevacizumab 10 mg/kg intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with interferon-alfa (IFN) 9 million units (MU) subcutaneous injection every 3 times a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.	

Reporting group values	Bevacizumab+Temsirrolimus	Bevacizumab+ Interferon-Alfa	Total
Number of subjects	400	391	791
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)	294	282	576
From 65-84 years	106	109	215
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.6	58.2	
standard deviation	± 10.1	± 10.4	-
Gender, Male/Female Units: participants			
Female	114	121	235
Male	286	270	556

End points

End points reporting groups

Reporting group title	Bevacizumab+Temsirolimus
Reporting group description:	
Bevacizumab 10 milligram per kilogram (mg/kg) intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with temsirolimus 25 mg intravenous infusion over at least 30 minutes once a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.	
Reporting group title	Bevacizumab+ Interferon-Alfa
Reporting group description:	
Bevacizumab 10 mg/kg intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with interferon-alfa (IFN) 9 million units (MU) subcutaneous injection every 3 times a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.	

Primary: Progression-Free Survival (PFS): Independent-Assessment

End point title	Progression-Free Survival (PFS): Independent-Assessment
End point description:	
PFS was defined as the interval from the date of randomization until the earlier date of progression or death. Progression was assessed by independent imaging reviewers using Response Evaluation Criteria in Solid Tumors (RECIST) criteria which is 20% increase in sum of longest diameter of target lesions from nadir (the smallest sum obtained previously); measurable increase in non-target lesion; appearance of new lesions. The efficacy endpoint analysis is conducted on ITT population (N=791).	
End point type	Primary
End point timeframe:	
Baseline until disease progression, initiation of new anticancer treatment, or death, assessed every 8 weeks (up to cut-off date: 19 April 2012)	

End point values	Bevacizumab+ Temsirolimus	Bevacizumab+ Interferon-Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	391		
Units: months				
median (confidence interval 95%)	9.1 (8.1 to 10.2)	9.3 (9 to 11.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
P value was based on 1-sided stratified log-rank test (stratification factors: prior nephrectomy [yes/no] and Memorial Sloan Kettering Cancer Center [MSKCC] risk factors [good/intermediate/poor] at time of randomization). The hazard ratio and corresponding 95 percent (%) confidence interval (CI) from the stratified Cox proportional hazards model were also presented.	
Comparison groups	Bevacizumab+Temsirolimus v Bevacizumab+ Interferon-Alfa

Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.3

Secondary: Progression-Free Survival (PFS): Investigator-Assessment

End point title	Progression-Free Survival (PFS): Investigator-Assessment
End point description:	
PFS was defined as the interval from the date of randomization until the earlier date of progression or death. Progression was assessed by investigator imaging reviewers using RECIST criteria which is 20% increase in sum of longest diameter of target lesions from nadir (the smallest sum obtained previously); measurable increase in non-target lesion; appearance of new lesions. The efficacy endpoint analysis is conducted on ITT population (N=791).	
End point type	Secondary
End point timeframe:	
Baseline until disease progression, initiation of new anticancer treatment, or death, assessed every 8 weeks (up to cut-off date: 19 April 2012)	

End point values	Bevacizumab+ Temsirolimus	Bevacizumab+ Interferon-Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	391		
Units: months				
median (confidence interval 95%)	9.1 (8.1 to 10.5)	10.8 (9.1 to 11.2)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
P-value was based on 1-sided stratified log-rank test (stratification factors: prior nephrectomy [yes/no] and MSKCC risk factors [good/intermediate/poor] at time of randomization). The hazard ratio and corresponding 95% CI from the stratified Cox proportional hazards model were also presented.	
Comparison groups	Bevacizumab+ Temsirolimus v Bevacizumab+ Interferon-Alfa

Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.4

Secondary: Percentage of Participants With Objective Response (complete response/partial response): Independent-Assessment

End point title	Percentage of Participants With Objective Response (complete response/partial response): Independent-Assessment
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End point description:

Percentage of participants with OR based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to RECIST. Confirmed response were those that persisted on repeat imaging study at least 4 weeks after initial documentation of response. CR was defined as disappearance of all lesions (target and/or non target). PR were those with at least 30% decrease in sum of the longest dimensions of target lesions taking as a reference the baseline sum longest dimensions, with non target lesions not increased or absent. The efficacy endpoint analysis is conducted on ITT population (N=791).

End point type	Secondary
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End point timeframe:

Baseline until disease progression, initiation of new anticancer treatment, or death, assessed every 8 weeks (up to cut-off date: 19 April 2012)

End point values	Bevacizumab+ Temeirolimus	Bevacizumab+ Interferon-Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	391		
Units: Percentage of participants				
number (confidence interval 95%)	27 (22.7 to 31.6)	27.4 (23 to 32.1)		

Statistical analyses

Statistical analysis title	Statistical analysis
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Statistical analysis description:

P-value (2-sided), risk ratio and associated 95% CI were based on Cochran-Mantel-Haenszel test stratified by prior nephrectomy and MSKCC risk group as randomized.

Comparison groups	Bevacizumab+Temeirolimus v Bevacizumab+ Interferon-Alfa
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Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.3

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to death due to any cause, censored at the last date known alive. Death was determined from adverse event data (where outcome was death) or from follow-up contact data (where the participant current status was death). The efficacy endpoint analysis is conducted on ITT population (N=791).	
End point type	Secondary
End point timeframe:	
Baseline until death due to any cause, assessed every 8 weeks (up to cut-off date: 19 April 2012)	

End point values	Bevacizumab+ Temsirolimus	Bevacizumab+ Interferon-Alfa		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	400	391		
Units: months				
median (confidence interval 95%)	25.8 (21.1 to 30.7)	25.5 (22.4 to 30.8)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
P value was based on 1-sided stratified log-rank test (stratification factors: prior nephrectomy [yes/no] and MSKCC risk factors [good/intermediate/poor] at time of randomization). The hazard ratio and corresponding 95% CI from the stratified Cox proportional hazards model were also presented.	
Comparison groups	Bevacizumab+ Temsirolimus v Bevacizumab+ Interferon-Alfa

Number of subjects included in analysis	791
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.3

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected and reported from the signing of the informed consent until end of treatment but no later than 30 days after the last dose of study medication.

Adverse event reporting additional description:

The same event may appear as both an AE and a SAE. However, what is presented are distinct events. An event may be categorized as serious in one participant and as nonserious in another participant, or one participant may have experienced both a serious and nonserious event during the study.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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Reporting groups

Reporting group title	Bevacizumab+ Interferon-Alfa
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Reporting group description:

Bevacizumab 10 mg/kg intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with interferon-alfa (IFN) 9 million units (MU) subcutaneous injection every 3 times a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.

Reporting group title	Bevacizumab+Temsirolimus
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Reporting group description:

Bevacizumab 10 milligram per kilogram (mg/kg) intravenous infusion over 90 minutes, 60 minutes or 30 minutes depending on the participant's tolerability every other week along with temsirolimus 25 mg intravenous infusion over at least 30 minutes once a week. Treatment was continued until disease progression, unacceptable toxicities, withdrawal of consent, or death.

Serious adverse events	Bevacizumab+ Interferon-Alfa	Bevacizumab+Temsirolimus	
Total subjects affected by serious adverse events			
subjects affected / exposed	158 / 391 (40.41%)	184 / 393 (46.82%)	
number of deaths (all causes)	239	261	
number of deaths resulting from adverse events	21	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to lung			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastasis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic pain			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic renal cell carcinoma			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Neoplasm progression			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 391 (0.26%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 12	0 / 11	
Tumour associated fever			

subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour ulceration			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 391 (0.26%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertension			

subjects affected / exposed	4 / 391 (1.02%)	6 / 393 (1.53%)	
occurrences causally related to treatment / all	6 / 6	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Peripheral Venous Disease			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Surgical and medical procedures			
Cancer Surgery			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	5 / 391 (1.28%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	7 / 12	1 / 5	
deaths causally related to treatment / all	0 / 3	0 / 2	
Chills			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (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	4 / 391 (1.02%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	2 / 5	0 / 2	
Disease progression			
subjects affected / exposed	16 / 391 (4.09%)	13 / 393 (3.31%)	
occurrences causally related to treatment / all	0 / 17	0 / 15	
deaths causally related to treatment / all	0 / 19	0 / 21	
Fatigue			
subjects affected / exposed	7 / 391 (1.79%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	7 / 7	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	6 / 391 (1.53%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	5 / 7	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 0	
Injury associated with device			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 391 (0.00%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Multi-organ failure			

subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 1	1 / 2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 391 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 391 (1.79%)	9 / 393 (2.29%)	
occurrences causally related to treatment / all	3 / 8	4 / 11	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden death			
subjects affected / exposed	0 / 391 (0.00%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	3 / 3	
Condition Aggravated			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atelectasis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	10 / 391 (2.56%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	2 / 12	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Epistaxis			
subjects affected / exposed	2 / 391 (0.51%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	3 / 391 (0.77%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	5 / 6	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hiccups			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal septum disorder			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal pain			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthopnoea			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 391 (0.51%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			

subjects affected / exposed	2 / 391 (0.51%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 391 (0.00%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 391 (1.02%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	7 / 8	3 / 7	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pulmonary hypertension			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 391 (0.26%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	1 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Sputum discoloured			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	3 / 391 (0.77%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	2 / 3	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 1	
Completed Suicide			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Investigations			
Blood pressure systolic decreased			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrin D dimer increased			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	2 / 391 (0.51%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Protein urine present			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Creatinine Increased			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Head injury			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (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	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	2 / 391 (0.51%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (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 coronary syndrome			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 391 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac valve disease			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 2	1 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary ostial stenosis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Brain stem infarction			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 391 (0.51%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	8 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 391 (0.77%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			

subjects affected / exposed	2 / 391 (0.51%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 391 (0.51%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Loss of consciousness			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental impairment			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Spinal cord compression			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	4 / 391 (1.02%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	4 / 391 (1.02%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Balance Disorder			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (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	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 391 (0.26%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Toxic Encephalopathy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Encephalopathy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 391 (3.07%)	10 / 393 (2.54%)	
occurrences causally related to treatment / all	10 / 31	7 / 12	
deaths causally related to treatment / all	2 / 2	0 / 0	
Disseminated intravascular coagulation			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous floaters			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 391 (1.53%)	8 / 393 (2.04%)	
occurrences causally related to treatment / all	1 / 8	0 / 8	
deaths causally related to treatment / all	0 / 2	0 / 1	
Anal fissure			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anal fistula			
subjects affected / exposed	2 / 391 (0.51%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Constipation			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 391 (1.28%)	7 / 393 (1.78%)	
occurrences causally related to treatment / all	1 / 6	9 / 9	
deaths causally related to treatment / all	0 / 1	0 / 1	
Gastric fistula			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 391 (0.26%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 2	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Painful defaecation			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	2 / 391 (0.51%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	1 / 2	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Rectal haemorrhage			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	2 / 391 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 391 (0.51%)	7 / 393 (1.78%)	
occurrences causally related to treatment / all	1 / 2	5 / 7	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 391 (0.00%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrectasia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	2 / 391 (0.51%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	3 / 391 (0.77%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	3 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 391 (0.51%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	2 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal impairment			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteral disorder			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Kidney Injury			
subjects affected / exposed	3 / 391 (0.77%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 5	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	1 / 391 (0.26%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Back pain			
subjects affected / exposed	3 / 391 (0.77%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	2 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bone lesion			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 391 (0.51%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	3 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 391 (0.26%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (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			
Abdominal abscess			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Abscess			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 391 (0.51%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal cellulitis			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	1 / 391 (0.26%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cellulitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Erysipelas			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhoid infection			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infection			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site infection			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			

subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung abscess			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 391 (0.51%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	1 / 1	0 / 3	
Pharyngitis			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 391 (1.28%)	16 / 393 (4.07%)	
occurrences causally related to treatment / all	0 / 7	1 / 24	
deaths causally related to treatment / all	0 / 2	2 / 8	
Post procedural infection			

subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 391 (0.26%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal abscess			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	4 / 391 (1.02%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	5 / 6	3 / 3	
deaths causally related to treatment / all	3 / 4	1 / 1	
Septic shock			
subjects affected / exposed	2 / 391 (0.51%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			

subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 391 (1.02%)	5 / 393 (1.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pharyngitis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmodium Malariae Infection			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Tuberculosis			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 391 (0.00%)	2 / 393 (0.51%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 391 (0.77%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
Diabetes mellitus			
subjects affected / exposed	1 / 391 (0.26%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 391 (0.26%)	0 / 393 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	2 / 391 (0.51%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	0 / 391 (0.00%)	4 / 393 (1.02%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 391 (0.77%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hyponatraemia			
subjects affected / exposed	2 / 391 (0.51%)	3 / 393 (0.76%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketosis			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 391 (0.00%)	1 / 393 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bevacizumab+ Interferon-Alfa	Bevacizumab+Temsilolimus	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	378 / 391 (96.68%)	383 / 393 (97.46%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	102 / 391 (26.09%)	128 / 393 (32.57%)	
occurrences (all)	307	427	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	113 / 391 (28.90%)	95 / 393 (24.17%)	
occurrences (all)	492	371	
Chills			
subjects affected / exposed	44 / 391 (11.25%)	15 / 393 (3.82%)	
occurrences (all)	95	18	
Fatigue			
subjects affected / exposed	122 / 391 (31.20%)	92 / 393 (23.41%)	
occurrences (all)	559	272	
Influenza like illness			
subjects affected / exposed	48 / 391 (12.28%)	14 / 393 (3.56%)	
occurrences (all)	335	17	
Mucosal inflammation			
subjects affected / exposed	40 / 391 (10.23%)	105 / 393 (26.72%)	
occurrences (all)	101	391	
Oedema peripheral			
subjects affected / exposed	32 / 391 (8.18%)	67 / 393 (17.05%)	
occurrences (all)	55	189	
Pyrexia			
subjects affected / exposed	154 / 391 (39.39%)	79 / 393 (20.10%)	
occurrences (all)	508	166	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	70 / 391 (17.90%)	79 / 393 (20.10%)	
occurrences (all)	191	160	
Dysphonia			
subjects affected / exposed	30 / 391 (7.67%)	13 / 393 (3.31%)	
occurrences (all)	52	34	
Dyspnoea			
subjects affected / exposed	49 / 391 (12.53%)	36 / 393 (9.16%)	
occurrences (all)	106	71	
Epistaxis			
subjects affected / exposed	82 / 391 (20.97%)	110 / 393 (27.99%)	
occurrences (all)	225	315	
Oropharyngeal pain			
subjects affected / exposed	16 / 391 (4.09%)	28 / 393 (7.12%)	
occurrences (all)	42	42	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	21 / 391 (5.37%)	7 / 393 (1.78%)	
occurrences (all)	39	16	
Depression			
subjects affected / exposed	22 / 391 (5.63%)	11 / 393 (2.80%)	
occurrences (all)	48	39	
Insomnia			
subjects affected / exposed	31 / 391 (7.93%)	28 / 393 (7.12%)	
occurrences (all)	65	66	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	35 / 391 (8.95%)	38 / 393 (9.67%)	
occurrences (all)	96	91	
Aspartate aminotransferase increased			
subjects affected / exposed	41 / 391 (10.49%)	33 / 393 (8.40%)	
occurrences (all)	125	69	
Blood creatinine increased			
subjects affected / exposed	25 / 391 (6.39%)	40 / 393 (10.18%)	
occurrences (all)	76	166	

Weight decreased subjects affected / exposed occurrences (all)	93 / 391 (23.79%) 346	90 / 393 (22.90%) 286	
Blood Alkaline Phosphatase Increased subjects affected / exposed occurrences (all)	14 / 391 (3.58%) 40	20 / 393 (5.09%) 51	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	37 / 391 (9.46%) 88	29 / 393 (7.38%) 49	
Dysgeusia subjects affected / exposed occurrences (all)	21 / 391 (5.37%) 62	33 / 393 (8.40%) 104	
Headache subjects affected / exposed occurrences (all)	82 / 391 (20.97%) 237	77 / 393 (19.59%) 182	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	66 / 391 (16.88%) 281	80 / 393 (20.36%) 326	
Leukopenia subjects affected / exposed occurrences (all)	40 / 391 (10.23%) 299	17 / 393 (4.33%) 61	
Lymphopenia subjects affected / exposed occurrences (all)	38 / 391 (9.72%) 268	24 / 393 (6.11%) 70	
Neutropenia subjects affected / exposed occurrences (all)	66 / 391 (16.88%) 369	18 / 393 (4.58%) 82	
Thrombocytopenia subjects affected / exposed occurrences (all)	40 / 391 (10.23%) 226	50 / 393 (12.72%) 167	
Ear and labyrinth disorders			
Vertigo subjects affected / exposed occurrences (all)	20 / 391 (5.12%) 45	4 / 393 (1.02%) 6	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	42 / 391 (10.74%)	48 / 393 (12.21%)	
occurrences (all)	79	82	
Abdominal pain upper			
subjects affected / exposed	21 / 391 (5.37%)	31 / 393 (7.89%)	
occurrences (all)	38	54	
Diarrhoea			
subjects affected / exposed	86 / 391 (21.99%)	126 / 393 (32.06%)	
occurrences (all)	200	254	
Constipation			
subjects affected / exposed	48 / 391 (12.28%)	43 / 393 (10.94%)	
occurrences (all)	96	80	
Gingival bleeding			
subjects affected / exposed	21 / 391 (5.37%)	5 / 393 (1.27%)	
occurrences (all)	61	23	
Haemorrhoids			
subjects affected / exposed	13 / 391 (3.32%)	28 / 393 (7.12%)	
occurrences (all)	21	82	
Nausea			
subjects affected / exposed	78 / 391 (19.95%)	69 / 393 (17.56%)	
occurrences (all)	210	123	
Stomatitis			
subjects affected / exposed	39 / 391 (9.97%)	102 / 393 (25.95%)	
occurrences (all)	89	292	
Toothache			
subjects affected / exposed	14 / 391 (3.58%)	37 / 393 (9.41%)	
occurrences (all)	16	57	
Vomiting			
subjects affected / exposed	53 / 391 (13.55%)	53 / 393 (13.49%)	
occurrences (all)	112	79	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	13 / 391 (3.32%)	27 / 393 (6.87%)	
occurrences (all)	29	62	
Pruritus			

subjects affected / exposed occurrences (all)	26 / 391 (6.65%) 70	60 / 393 (15.27%) 144	
Rash subjects affected / exposed occurrences (all)	32 / 391 (8.18%) 91	126 / 393 (32.06%) 392	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	111 / 391 (28.39%) 571	143 / 393 (36.39%) 727	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	49 / 391 (12.53%) 118	52 / 393 (13.23%) 102	
Back pain subjects affected / exposed occurrences (all)	53 / 391 (13.55%) 125	47 / 393 (11.96%) 115	
Bone pain subjects affected / exposed occurrences (all)	22 / 391 (5.63%) 57	18 / 393 (4.58%) 58	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	19 / 391 (4.86%) 49	27 / 393 (6.87%) 62	
Musculoskeletal pain subjects affected / exposed occurrences (all)	28 / 391 (7.16%) 47	14 / 393 (3.56%) 32	
Myalgia subjects affected / exposed occurrences (all)	60 / 391 (15.35%) 178	19 / 393 (4.83%) 28	
Pain in extremity subjects affected / exposed occurrences (all)	35 / 391 (8.95%) 72	43 / 393 (10.94%) 101	
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	15 / 391 (3.84%) 28	20 / 393 (5.09%) 34	
Urinary tract infection			

subjects affected / exposed occurrences (all)	21 / 391 (5.37%) 38	23 / 393 (5.85%) 38	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	127 / 391 (32.48%)	103 / 393 (26.21%)	
occurrences (all)	415	309	
Hypercholesterolaemia			
subjects affected / exposed	39 / 391 (9.97%)	126 / 393 (32.06%)	
occurrences (all)	144	578	
Hyperglycaemia			
subjects affected / exposed	19 / 391 (4.86%)	86 / 393 (21.88%)	
occurrences (all)	50	332	
Hyperkalaemia			
subjects affected / exposed	37 / 391 (9.46%)	29 / 393 (7.38%)	
occurrences (all)	145	85	
Hypocalcaemia			
subjects affected / exposed	13 / 391 (3.32%)	24 / 393 (6.11%)	
occurrences (all)	57	74	
Hypertriglyceridaemia			
subjects affected / exposed	82 / 391 (20.97%)	114 / 393 (29.01%)	
occurrences (all)	399	587	
Hypomagnesaemia			
subjects affected / exposed	16 / 391 (4.09%)	20 / 393 (5.09%)	
occurrences (all)	34	37	
Hyponatraemia			
subjects affected / exposed	21 / 391 (5.37%)	23 / 393 (5.85%)	
occurrences (all)	47	88	
Hypophosphataemia			
subjects affected / exposed	18 / 391 (4.60%)	40 / 393 (10.18%)	
occurrences (all)	44	123	
Hypokalaemia			
subjects affected / exposed	4 / 391 (1.02%)	20 / 393 (5.09%)	
occurrences (all)	7	49	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2008	Protocol amendment 1 included minor clarifications to inclusion/exclusion criteria and study required assessments. Long-Term Follow-up no longer required as part of the study. Protocol-defined tumor assessments were no longer required, rather assessments were performed according to local standard of care at the discretion of the treating investigator. Tumor assessments no longer required to be submitted to the independent imaging vendor. Plasma samples for biomarker analysis were no longer required. Health Outcome questionnaires were no longer required. Serious adverse events (SAEs) of which the investigator became aware of after the active safety reporting period should be reported to Pfizer with certain exceptions. Appendix regarding Crossover in response to E-DMC Recommendation to prematurely discontinue the Bevacizumab + Temsirolimus arm was deleted. Final OS analysis as stated in Amendment 3 (15 December 2011) eliminated. Use of the External Data Monitoring Committee (E-DMC) was no longer required.
22 March 2010	Protocol Amendment 2 included an interim analysis. Sponsor and Study Team information removed; Document History section added; Abbreviations and definitions sections revised; Single Reference Safety Document (SRSD) is the investigator's brochure for temsirolimus and the product label for bevacizumab and interferon-alfa (various sections); Clarification added in subject selection as to collection of retrospective data; Clinical Operations Randomization Environment (CORE) system language regarding subject discontinuation removed. Language regarding preparation and dispensing Updated Medication Errors language to align with EU CT3 added. Updated language as to drug storage conditions. Revised language as to Electronic Case Report Form documentation of Adverse Event. Updated Subject withdrawal language; Added language regarding required assessments when not performed; updated due to alignment with EU CT3 guidance (effective 11 June 2011) and US FDA (Food and Drug Administration) Final Rule (effective 28 September 2011) and more specifically adverse event follow-up clarified to align with CT3 and Final Rule. Active reporting period and necessity to report all SAEs post-active reporting period clarifying language added to align with CT3 and Final Rule. Definition of AE updated to align under CT3 guidance and revised Pfizer corporate policy AEM01, including addition of medication error.
09 December 2011	Protocol Amendment 3 included alignment of the SAE reporting criteria with EU-CT3 and US FDA final rule guidances. Addition of an Interim Analysis which was planned at approximately 236 observed events (corresponding to 50% information) and recommendation to stop the trial early was given for futility only. The endpoint used at the interim analysis would be the investigator-assessed PFS (tumor progression + death only excluding symptomatic deterioration).
07 November 2012	Protocol amendment 4 included the results of the primary analysis, revised study flowchart and long-term follow-up was removed, Plasma samples and tumor tissue were collected for biomarker samples and health outcome questionnaires. Participants (men and women) must be agreed to use medically accepted contraceptive methods during the treatment phase and for 6 months after the last dose of bevacizumab. Participants with a history of cervical carcinoma in situ (CIS) or breast ductal CIS or breast lobular CIS were considered eligible provided they have completed definitive therapy. Participants developing tracheo-oesophageal fistulae or any grade 4 fistula were permanently removed from the treatment phase. The sponsor might request to perform additional unscheduled survival contacts, or to shift the schedule of survival data collection, if needed for data analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported