Clinical trial results:
Phase III study comparing maintenance by pemetrexed or gemcitabine to surveillance in elderly patient (70 year old) with advanced Non Small Cell Lung Cancer controlled by induction chemotherapy

Summary

EudraCT number	2012-005520-15
Trial protocol	FR
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	26 January 2023
First version publication date	26 January 2023

Trial information

Trial identification

Sponsor protocol code	IFCT-1201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01850303
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IFCT
Sponsor organisation address	10 Rue de la Grange Batelière , Paris, France, 75009
Public contact	Contact, IFCT, 33 1.56.81.10.46, contact@ifct.fr
Scientific contact	Contact, IFCT, 33 1.56.81.10.46, contact@ifct.fr

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	01 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Overall survival of patients whose disease is controlled after induction chemotherapy with 4 cycles of carboplatin and paclitaxel weekly from randomization maintenance versus observation.

Protection of trial subjects:

Algorithms for management of adverse events were provided in the protocol.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 627
Worldwide total number of subjects	627
EEA total number of subjects	627

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)	0
From 65 to 84 years	601
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

632 patients were enrolled from May 2013 to October 2016. Of the 328 (52.3%) patients randomised after induction therapy, 166 patients were assigned to the observation arm, versus 162 to the switch maintenance arm, 119 of whom received pemetrexed and 43 gemcitabine.

Pre-assignment

Screening details:

Patients should have a histologically/cytologically confirmed stage IV or III not amenable to surgery or radiotherapy NSCLC, an age between 70 and 89 years, a performance status (PS) 0-2, a mini-mental score (MMS) > 23/30 and appropriate hepatic and renal functions and haematopoietic reserves.

Period 1

Period 1 title	Induction
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Paclitaxel - Carboplatin

Arm description: -

Arm type	Induction
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel IV 90 mg/m² at D1, D8, D15 ; cycles repeated every 28 days.

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

Dosage and administration details:

Carboplatin IV AUC6 (D1= D29); cycles repeated every 28 days.

Number of subjects in period 1	Paclitaxel - Carboplatin
Started	627
Completed	328
Not completed	299
Consent withdrawn by subject	19
Physician decision	2
Adverse event, non-fatal	39
Death	53

Not specified	11
Performans status >2	12
Treatment not received	4
Lack of efficacy	159

Period 2	
Period 2 title	Maintenance
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Arm A - Follow-up

Arm description: -

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Arm B1 - Maintenance Pemetrexed

Arm description:

Pemetrexed for patients with non-squamous cell carcinoma

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Maintenance switch with pemetrexed IV 500 mg/m2 every 3 weeks until progression or toxicity.

Arm title	ARM B2 - Maintenance Gemcitabine

Arm description:

Gemcitabine for patients with squamous cell carcinoma

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Maintenance switch with gemcitabine monotherapy IV (1150 mg/m² on Day 1, Day 8, cycles repeated every 21 days) until progression or unacceptable toxicity

Arm title	ARM B - Maintenance

Arm description:

Pemetrexed for patients with non-squamous cell carcinoma
Gemcitabine for patients with squamous cell carcinoma

Arm type	Experimental
Investigational medicinal product name	Pemetrexed
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Maintenance switch with pemetrexed IV 500 mg/m2 every 3 weeks until progression or toxicity.

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

Dosage and administration details:

Maintenance switch with gemcitabine monotherapy IV (1150 mg/m² on Day 1, Day 8, cycles repeated every 21 days) until progression or unacceptable toxicity

Number of subjects in period 2	Arm A - Follow-up	Arm B1 - Maintenance Pemetrexed	ARM B2 - Maintenance Gemcitabine
Started	166	119	43
Completed	166	109	43
Not completed	0	10	0
Not received treatment	-	-	-
Not received Pemetrexed	-	10	-

Number of subjects in period 2	ARM B - Maintenance
Started	162
Completed	152
Not completed	10
Not received treatment	10
Not received Pemetrexed	-

Period 3

Period 3 title	Second line Erlotinib
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Erlotinib

Arm description:

Second line fixed with erlotinib in case of disease progression (RECIST 1.1).

Arm type	Second line fixed with erlotinib
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib 150 mg/day

Number of subjects in period 3	Erlotinib
Started	173
Completed	173

Baseline characteristics

Reporting groups	
Reporting group title	Induction

Reporting group description: -

Reporting group values	Induction	Total	
Number of subjects	627	627	
Age categorical Units: Subjects			
From 70 to 79	486	486	
From 80 to 89	141	141	
Age continuous Units: years			
median	76.4		
full range (min-max)	70.0 to 89.4	-	
Gender categorical Units: Subjects			
Female	152	152	
Male	475	475	
Performans status (PS) Units: Subjects			
PS 0-1	535	535	
PS 2	86	86	
Not evaluated	6	6	
Stage Units: Subjects			
Stage III	62	62	
Stage IV	565	565	
Smocking status Units: Subjects			
Smoker	535	535	
Never Smocker	92	92	
Histology subtype Units: Subjects			
Adenocarcinoma	401	401	
Squamous cell	178	178	
Large Cell	13	13	
NOS	26	26	
Other	9	9	
Mini Mental Score (MMS) Units: MMS score			
median	28.0		
full range (min-max)	19.0 to 30.0	-	

End points

End points reporting groups

Reporting group title	Paclitaxel - Carboplatin
Reporting group description: -	
Reporting group title	Arm A - Follow-up
Reporting group description: -	
Reporting group title	Arm B1 - Maintenance Pemetrexed
Reporting group description: Pemetrexed for patients with non-squamous cell carcinoma	
Reporting group title	ARM B2 - Maintenance Gemcitabine
Reporting group description: Gemcitabine for patients with squamous cell carcinoma	
Reporting group title	ARM B - Maintenance
Reporting group description: Pemetrexed for patients with non-squamous cell carcinoma Gemcitabine for patients with squamous cell carcinoma	
Reporting group title	Erlotinib
Reporting group description: Second line fixed with erlotinib in case of disease progression (RECIST 1.1).	

Primary: Overall survival

End point title	Overall survival
End point description: Time from randomisation to death from any cause.	
End point type	Primary
End point timeframe: 39.7 months (median follow-up)	

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	162		
Units: months				
median (confidence interval 95%)	14.1 (12.0 to 17.0)	14.0 (10.9 to 16.9)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: Time from randomisation to death from any cause.	
Comparison groups	Arm A - Follow-up v ARM B - Maintenance

Number of subjects included in analysis	328
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.2
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Number of maintenance cycles received

End point title	Number of maintenance cycles received

End point description:

End point type	Secondary

End point timeframe:

39.7 months (median follow-up)

End point values	Arm B1 - Maintenance Pemetrexed	ARM B2 - Maintenance Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	43		
Units: number of cycles				
median (full range (min-max))	4 (1 to 38)	4 (1 to 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free survival

End point title	Progression Free survival

End point description:

End point type	Secondary

End point timeframe:

39.7 months (median follow-up)

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	162		
Units: months				
median (full range (min-max))	2.7 (2.6 to 3.1)	5.7 (4.8 to 7.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response from randomization

End point title	Duration of response from randomization

End point description:

Duration of the response or stabilization obtained from the maintenance therapy.

End point type	Secondary

End point timeframe:

39.7 months (median follow-up)

End point values	Arm A - Follow-up	Arm B1 - Maintenance Pemetrexed	ARM B2 - Maintenance Gemcitabine	ARM B - Maintenance
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	166	119	43	162
Units: months				
median (full range (min-max))	2.7 (0 to 41.8)	5.6 (0 to 45.8)	6.8 (0 to 36.9)	5.7 (0 to 45.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Patients receiving second line erlotinib

End point title	Patients receiving second line erlotinib

End point description:

End point type	Secondary

End point timeframe:

39.7 months (median follow-up)

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	162		
Units: Number of subjects	109	68		

Statistical analyses

No statistical analyses for this end point

Secondary: Evalutation of clinical prognostic survival factors

End point title	Evalutation of clinical prognostic survival factors

End point description:

Univariate analysis of all stratification criteria for randomization.
0 to 1 : in favor of maintenance arm
1 to 2 : in favor of follow-up arm

End point type	Secondary

End point timeframe:

39.7 months (median follow-up)

End point values	Paclitaxel - Carboplatin			
Subject group type	Reporting group			
Number of subjects analysed	627			
Units: Hazard Ratio				
number (confidence interval 95%)				
ALL	0.91 (0.71 to 1.17)			
ECOG Performans Status 0-1	1.03 (0.78 to 1.36)			
ECOG Performans Status 2	0.70 (0.40 to 1.23)			
Non-squamous cell carcinoma	0.82 (0.61 to 1.09)			
Squamous cell carcinoma	1.26 (0.78 to 2.05)			
Stable response after 4 cycles	0.94 (0.67 to 1.33)			
Objective response after 4 cycles	0.97 (0.68 to 1.39)			
Age : 80 years old and over	1.01 (0.58 to 1.74)			
Age : < 80 years old	0.90 (0.68 to 1.18)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Response rate according to RECIST 1.1 - Second line

End point title	Response rate according to RECIST 1.1 - Second line

End point description:

End point type	Post-hoc

End point timeframe:

39.7 months (median follow-up)

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[1]	103[2]		
Units: Number of subjects				
Complete response	1	1		
Partial response	8	7		
Stable	40	30		
Progression	61	42		
Not done/Not evaluable	5	5		
Missing	18	18		

Notes:

[1] - Patients with second-line systemic post-treatment

[2] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival from second line

End point title	Overall Survival from second line

End point description:

End point type	Post-hoc

End point timeframe:

39.7 months (median follow-up)

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[3]	103[4]		
Units: months				
median (confidence interval 95%)	11.7 (8.8 to 14.9)	9.2 (5.9 to 13.2)		

Notes:
[3] - Patients with second-line systemic post-treatment
[4] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression Free survival from second line

End point title	Progression Free survival from second line

End point description:

End point type	Post-hoc

End point timeframe:
39.7 months (median follow-up)

End point values	Arm A - Follow-up	ARM B - Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133[5]	103[6]		
Units: Months				
median (confidence interval 95%)	2.9 (2.1 to 4)	3.2 (2.2 to 4.8)		

Notes:
[5] - Patients with second-line systemic post-treatment
[6] - Patients with second-line systemic post-treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The adverse events have to be reported from inclusion to 30 day following the end of administration of study treatments.

Adverse event reporting additional description:

The maximal grade of adverse events was collected by cycle of treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Induction

Reporting group description: -

Reporting group title	Arm A - Follow-up

Reporting group description: -

Reporting group title	Arm B1 - Maintenance Pemetrexed

Reporting group description:

The safety population - Arm B Pemetrexed will be defined as all patients who received at least one dose of pemetrexed.

Reporting group title	Arm B2 - Maintenance Gemcitabine

Reporting group description:

The safety population - Arm B Gemcitabine will be defined as all patients who received at least one dose of Gemcitabine.

Serious adverse events	Induction	Arm A - Follow-up	Arm B1 - Maintenance Pemetrexed
Total subjects affected by serious adverse events			
subjects affected / exposed	220 / 623 (35.31%)	2 / 166 (1.20%)	38 / 109 (34.86%)
number of deaths (all causes)	53	134	93
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertension			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	11 / 623 (1.77%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 11	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 623 (1.44%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	5 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0

Chest pain			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 5	0 / 0	0 / 2
General physical health deterioration			
subjects affected / exposed	34 / 623 (5.46%)	1 / 166 (0.60%)	8 / 109 (7.34%)
occurrences causally related to treatment / all	14 / 37	0 / 1	3 / 8
deaths causally related to treatment / all	0 / 15	0 / 0	0 / 2
Generalised oedema			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Oedema			

subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sense of oppression			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	4 / 623 (0.64%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	13 / 623 (2.09%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 15	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 2
Epistaxis			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	4 / 623 (0.64%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemothorax			

subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Laryngeal dyspnoea			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	12 / 623 (1.93%)	0 / 166 (0.00%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	5 / 12	0 / 0	1 / 6
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 2
Pleural effusion			
subjects affected / exposed	9 / 623 (1.44%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 12	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			

subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	7 / 623 (1.12%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 4	0 / 0	0 / 1
Respiratory failure			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mania			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	7 / 623 (1.12%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	7 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Injury, poisoning and procedural			

complications			
Abdominal injury			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis chemical			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			

subjects affected / exposed	7 / 623 (1.12%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	1 / 8	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coma			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Facial nerve disorder			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor dysfunction			

subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paralysis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 623 (2.09%)	0 / 166 (0.00%)	6 / 109 (5.50%)
occurrences causally related to treatment / all	11 / 13	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	6 / 623 (0.96%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	3 / 3	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	12 / 623 (1.93%)	0 / 166 (0.00%)	3 / 109 (2.75%)
occurrences causally related to treatment / all	13 / 13	0 / 0	3 / 3
deaths causally related to treatment / all	3 / 3	0 / 0	2 / 2
Neutropenia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	5 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	3 / 3	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	7 / 623 (1.12%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	4 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 1
Inguinal hernia			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Melaena			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	3 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	3 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hydrocholecystis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin toxicity			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 623 (0.96%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	5 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Back pain			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	4 / 623 (0.64%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	4 / 623 (0.64%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium colitis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes virus infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	6 / 623 (0.96%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	5 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 623 (0.64%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	2 / 623 (0.32%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	22 / 623 (3.53%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	14 / 22	0 / 0	1 / 1
deaths causally related to treatment / all	5 / 11	0 / 0	1 / 1
Septic shock			
subjects affected / exposed	6 / 623 (0.96%)	1 / 166 (0.60%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	6 / 6	0 / 1	1 / 1
deaths causally related to treatment / all	2 / 2	0 / 1	1 / 1
Staphylococcal infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	5 / 623 (0.80%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	3 / 623 (0.48%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			

subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 623 (0.00%)	0 / 166 (0.00%)	1 / 109 (0.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	0 / 109 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Arm B2 - Maintenance Gemcitabine		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 43 (55.81%)		
number of deaths (all causes)	31		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Venous thrombosis			

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza like illness			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malaise			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oedema peripheral				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Sense of oppression				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic shock				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchospasm			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epistaxis			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypercapnia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Laryngeal dyspnoea				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	3 / 43 (6.98%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Psychiatric disorders				
Confusional state				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Haemoglobin decreased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Abdominal injury				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis chemical				

subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural complication				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skull fracture				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	4 / 43 (9.30%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Cardiomyopathy				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coma			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial nerve disorder			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Motor dysfunction				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorder				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paralysis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral sensory neuropathy				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	2 / 43 (4.65%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Bone marrow failure				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Febrile bone marrow aplasia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hydrocholecystis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin toxicity			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Urinary retention				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rheumatoid arthritis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Infections and infestations			
Abscess			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Catheter site infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium colitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes virus infection			

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 43 (6.98%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Prostate infection				

subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 43 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoalbuminaemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Induction	Arm A - Follow-up	Arm B1 - Maintenance Pemetrexed
Total subjects affected by non-serious adverse events			
subjects affected / exposed	602 / 623 (96.63%)	135 / 166 (81.33%)	106 / 109 (97.25%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	318 / 623 (51.04%)	42 / 166 (25.30%)	57 / 109 (52.29%)
occurrences (all)	320	58	118
Chest pain			
subjects affected / exposed	36 / 623 (5.78%)	12 / 166 (7.23%)	7 / 109 (6.42%)
occurrences (all)	38	12	8
Fatigue			
subjects affected / exposed	34 / 623 (5.46%)	4 / 166 (2.41%)	8 / 109 (7.34%)
occurrences (all)	34	5	12
General physical health deterioration			
subjects affected / exposed	37 / 623 (5.94%)	2 / 166 (1.20%)	16 / 109 (14.68%)
occurrences (all)	39	2	17
Oedema peripheral			
subjects affected / exposed	51 / 623 (8.19%)	5 / 166 (3.01%)	30 / 109 (27.52%)
occurrences (all)	52	8	65
Pyrexia			
subjects affected / exposed	30 / 623 (4.82%)	3 / 166 (1.81%)	15 / 109 (13.76%)
occurrences (all)	30	5	23
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	106 / 623 (17.01%)	33 / 166 (19.88%)	16 / 109 (14.68%)
occurrences (all)	106	43	23
Dyspnoea			
subjects affected / exposed	159 / 623 (25.52%)	40 / 166 (24.10%)	30 / 109 (27.52%)
occurrences (all)	159	52	52
Lung disorder			
subjects affected / exposed	12 / 623 (1.93%)	0 / 166 (0.00%)	6 / 109 (5.50%)
occurrences (all)	12	0	6
Productive cough			
subjects affected / exposed	24 / 623 (3.85%)	3 / 166 (1.81%)	8 / 109 (7.34%)
occurrences (all)	24	3	8

Chest pain			
subjects affected / exposed	5 / 623 (0.80%)	4 / 166 (2.41%)	1 / 109 (0.92%)
occurrences (all)	5	4	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	15 / 623 (2.41%)	0 / 166 (0.00%)	13 / 109 (11.93%)
occurrences (all)	15	0	21
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 623 (3.53%)	0 / 166 (0.00%)	19 / 109 (17.43%)
occurrences (all)	22	0	27
Blood alkaline phosphatase increased			
subjects affected / exposed	21 / 623 (3.37%)	0 / 166 (0.00%)	8 / 109 (7.34%)
occurrences (all)	21	0	11
Gamma-glutamyltransferase increased			
subjects affected / exposed	32 / 623 (5.14%)	3 / 166 (1.81%)	11 / 109 (10.09%)
occurrences (all)	33	5	12
Weight decreased			
subjects affected / exposed	78 / 623 (12.52%)	6 / 166 (3.61%)	11 / 109 (10.09%)
occurrences (all)	78	6	16
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	8 / 623 (1.28%)	0 / 166 (0.00%)	2 / 109 (1.83%)
occurrences (all)	8	0	2
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	60 / 623 (9.63%)	18 / 166 (10.84%)	9 / 109 (8.26%)
occurrences (all)	60	29	18
Paraesthesia			
subjects affected / exposed	97 / 623 (15.57%)	14 / 166 (8.43%)	17 / 109 (15.60%)
occurrences (all)	103	23	23
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	449 / 623 (72.07%)	62 / 166 (37.35%)	81 / 109 (74.31%)
occurrences (all)	450	79	186
Febrile neutropenia			

subjects affected / exposed	17 / 623 (2.73%)	0 / 166 (0.00%)	8 / 109 (7.34%)
occurrences (all)	17	0	8
Leukopenia			
subjects affected / exposed	79 / 623 (12.68%)	0 / 166 (0.00%)	11 / 109 (10.09%)
occurrences (all)	79	0	16
Lymphopenia			
subjects affected / exposed	68 / 623 (10.91%)	5 / 166 (3.01%)	11 / 109 (10.09%)
occurrences (all)	68	8	16
Neutropenia			
subjects affected / exposed	363 / 623 (58.27%)	6 / 166 (3.61%)	50 / 109 (45.87%)
occurrences (all)	370	6	88
Thrombocytopenia			
subjects affected / exposed	277 / 623 (44.46%)	6 / 166 (3.61%)	41 / 109 (37.61%)
occurrences (all)	279	7	65
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	13 / 109 (11.93%)
occurrences (all)	1	0	21
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	100 / 623 (16.05%)	4 / 166 (2.41%)	16 / 109 (14.68%)
occurrences (all)	100	6	24
Diarrhoea			
subjects affected / exposed	117 / 623 (18.78%)	3 / 166 (1.81%)	15 / 109 (13.76%)
occurrences (all)	118	3	21
Nausea			
subjects affected / exposed	172 / 623 (27.61%)	2 / 166 (1.20%)	28 / 109 (25.69%)
occurrences (all)	175	2	42
Vomiting			
subjects affected / exposed	76 / 623 (12.20%)	1 / 166 (0.60%)	11 / 109 (10.09%)
occurrences (all)	60	1	15
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	90 / 623 (14.45%)	6 / 166 (3.61%)	3 / 109 (2.75%)
occurrences (all)	90	9	7
Pruritus			

subjects affected / exposed	11 / 623 (1.77%)	2 / 166 (1.20%)	7 / 109 (6.42%)
occurrences (all)	11	3	8
Rash			
subjects affected / exposed	9 / 623 (1.44%)	3 / 166 (1.81%)	9 / 109 (8.26%)
occurrences (all)	9	3	12
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	66 / 623 (10.59%)	15 / 166 (9.04%)	25 / 109 (22.94%)
occurrences (all)	66	22	56
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	36 / 623 (5.78%)	10 / 166 (6.02%)	5 / 109 (4.59%)
occurrences (all)	41	11	7
Back pain			
subjects affected / exposed	33 / 623 (5.30%)	12 / 166 (7.23%)	14 / 109 (12.84%)
occurrences (all)	33	17	17
Musculoskeletal pain			
subjects affected / exposed	10 / 623 (1.61%)	0 / 166 (0.00%)	4 / 109 (3.67%)
occurrences (all)	10	0	6
Pain in extremity			
subjects affected / exposed	21 / 623 (3.37%)	7 / 166 (4.22%)	5 / 109 (4.59%)
occurrences (all)	21	7	6
Infections and infestations			
Bronchitis			
subjects affected / exposed	20 / 623 (3.21%)	7 / 166 (4.22%)	11 / 109 (10.09%)
occurrences (all)	21	7	14
Conjunctivitis			
subjects affected / exposed	3 / 623 (0.48%)	1 / 166 (0.60%)	9 / 109 (8.26%)
occurrences (all)	3	1	15
Erysipelas			
subjects affected / exposed	1 / 623 (0.16%)	0 / 166 (0.00%)	10 / 109 (9.17%)
occurrences (all)	1	0	17
Lung infection			
subjects affected / exposed	9 / 623 (1.44%)	5 / 166 (3.01%)	7 / 109 (6.42%)
occurrences (all)	9	7	7
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	133 / 623 (21.35%)	8 / 166 (4.82%)	26 / 109 (23.85%)
occurrences (all)	135	10	41
Hypoalbuminaemia			
subjects affected / exposed	41 / 623 (6.58%)	6 / 166 (3.61%)	10 / 109 (9.17%)
occurrences (all)	41	6	16
Hypocalcaemia			
subjects affected / exposed	42 / 623 (6.74%)	3 / 166 (1.81%)	7 / 109 (6.42%)
occurrences (all)	42	4	9
Hypokalaemia			
subjects affected / exposed	16 / 623 (2.57%)	2 / 166 (1.20%)	6 / 109 (5.50%)
occurrences (all)	16	2	7
Hyponatraemia			
subjects affected / exposed	35 / 623 (5.62%)	1 / 166 (0.60%)	4 / 109 (3.67%)
occurrences (all)	35	1	9
Hyperglycaemia			
subjects affected / exposed	31 / 623 (4.98%)	4 / 166 (2.41%)	3 / 109 (2.75%)
occurrences (all)	31	5	3

Non-serious adverse events	Arm B2 - Maintenance Gemcitabine		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 43 (97.67%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 43 (37.21%)		
occurrences (all)	25		
Chest pain			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	12		
General physical health deterioration			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Oedema peripheral			

subjects affected / exposed	8 / 43 (18.60%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	9 / 43 (20.93%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 43 (25.58%)		
occurrences (all)	18		
Dyspnoea			
subjects affected / exposed	14 / 43 (32.56%)		
occurrences (all)	20		
Lung disorder			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	0 / 43 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	9		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	6		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	3		
Weight decreased			

subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 4		
Cardiac disorders Cardiac failure subjects affected / exposed occurrences (all)	 4 / 43 (9.30%) 4		
Nervous system disorders Neuropathy peripheral subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	 5 / 43 (11.63%) 15 6 / 43 (13.95%) 20		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 34 / 43 (79.07%) 77 2 / 43 (4.65%) 2 6 / 43 (13.95%) 7 8 / 43 (18.60%) 12 19 / 43 (44.19%) 25 23 / 43 (53.49%) 38		
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	 0 / 43 (0.00%) 0		
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	3 / 43 (6.98%) 3 2 / 43 (4.65%) 2 1 / 43 (2.33%) 3 1 / 43 (2.33%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 2 / 43 (4.65%) 2 1 / 43 (2.33%) 1 1 / 43 (2.33%) 3		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 5 / 43 (11.63%) 11		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 2 / 43 (4.65%) 5 3 / 43 (6.98%) 3 3 / 43 (6.98%) 3		

Pain in extremity subjects affected / exposed occurrences (all)	4 / 43 (9.30%) 5		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Erysipelas subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all)	 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 2 / 43 (4.65%) 2 3 / 43 (6.98%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all) Hypocalcaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	 4 / 43 (9.30%) 8 3 / 43 (6.98%) 5 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 0 / 43 (0.00%) 0 3 / 43 (6.98%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2013	- Clarification of inclusion/exclusion criteria * Patients with active or symptomatic central nervous system metastases are ineligible. Patients with a history of symptomatic central nervous system metastases or spinal cord compression may be included if they have been treated (surgery or radiotherapy) and have become asymptomatic. Oral corticosteroids are allowed provided that the dose has been stable for at least 4 weeks prior to the start of treatment. * The criterion for radiation therapy is moved to maintenance eligibility criteria and updated for: "No concurrent radiation therapy, except for palliative localized non-spinal bone radiation therapy, with a 2 week delay between the administration of gemcitabine and the start of radiation therapy or the end of radiation therapy before the start of treatment, which may be shortened to 8 days if required by the patient's clinical condition. In the case of spinal irradiation, irradiation should be avoided as much as possible within 4 weeks after the administration of gemcitabine." - Clarification of the time frame to start treatment: the maximum time between inclusion and the start of induction treatment is 2 weeks. The maximum time between Day 1 of the 4th cycle of induction therapy and Day 1 of maintenance is 42 days. The second line should start no later than 3 weeks after the assessment showing progression. - Correction of the summary table of examinations: * Deletion of the geriatric depression scale at each evaluation (to be done only at inclusion and after 4 cycles of induction). * Biology at Day 8 and Day 15 are only to be done for patients receiving chemotherapy. - Chemotherapy doses will be capped at 400 mg/m² for carboplatin and at 2m² of body surface area in general. - Calvert's formula will be used for calculation of carboplatin dose.
18 August 2014	- Correction of the criterion on peripheral neuropathy (possible inclusion of patients with grade 1 neuropathy). - Patients with a history of prostate cancer less than 5 years old may be included under certain conditions. - Clarification of the tumor assessment at randomization: thoracic CT with adrenal sections, abdominal ultrasound and/or abdominal CT and brain CT or MRI are to be performed at randomization (those exams will be the reference for assessment during maintenance and observation).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Choice of the geriatric indexes was somewhat arbitrary ; Relatively high number of missing values pertaining to the geriatric indexes at the time of randomisation ; Erlotinib is no longer recommended as salvage therapy in pts without EGFR mutations

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32898792