Clinical trial results:
A randomised, phase II trial to evaluate a treatment with Tyrosine Kinase Inhibitor of Epidermal Growth Factor (EGFR-TKI) versus EGFR-TKI associated with an anti-estrogen treatment (fulvestrant) in women with an advanced stage of non squamous non small cell lung cancer

Summary

EudraCT number	2011-003571-11
Trial protocol	FR
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	02 February 2023
First version publication date	02 February 2023

Trial information

Trial identification

Sponsor protocol code	IFCT-1003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01556191
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	IFCT, IFCT, 33 156811045, contact@ifct.fr
Scientific contact	IFCT, IFCT, 33 156811045, 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 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

3-months progression free survival for patient with EGFR mutation
9-months progression free survival for patient with EGFR wild type

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	15 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 379
Worldwide total number of subjects	379
EEA total number of subjects	379

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)	177
From 65 to 84 years	196
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

379 patients included.
204 patients (gefitinib 104 and G+Fulvestrant 100) and 175 patients (erlotinib 87 and E+Fulvestrant 88) were enrolled in the EGFR mutated and EGFR-WT cohorts respectively.

Pre-assignment

Screening details:

Main inclusion criteria were histologically confirmed inoperable stage III or stage IV nonsquamous NSCLCs, the presence of at least one lesion that could be measured by a CT scan (RECIST v1.1), postmenopausal female (either >60 year or amenorrhea >12 months), with a World Health Organization performance index of 0, 1, or 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	A1 - EGFR mut Gefitinib

Arm description:

EGFR mutated patients receiving Gefitinib.

Arm type	Experimental
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	Iressa
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Gefitinib is administered orally in a 250 mg tablet (single dose) / day

Arm title	B1 - EGFR mut Gefitinib Fulvestrant

Arm description:

EGFR mutated patients receiving Gefitinib + Fulvestrant

Arm type	Experimental
Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	Iressa
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Gefitinib is administered orally in a 250 mg tablet (single dose) / day

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Prefilled syringe of 5 ml (250 mg of fulvestrant) :

Two slow, intramuscular injections (2 x 250 mg) by month with an additional 500 mg dose two weeks after the initial dose. 5 ml in each buttock with prefilled syringes.

Arm title	A2 - EGFR WT Erlotinib
Arm description: EGFR WT patients receiving Erlotinib.	
Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Erlotinib is administered orally in a 150 mg tablet (also available in 25 and 100 mg), to be taken on an empty stomach (one hour before or two hours after eating) by day.	
Arm title	B2 - EGFR WT Erlotinib Fulvestrant
Arm description: EGFR WT patients receiving Erlotinib + Fulvestrant	
Arm type	Experimental
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: Erlotinib is administered orally in a 150 mg tablet (also available in 25 and 100 mg), to be taken on an empty stomach (one hour before or two hours after eating) by day.	
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	Faslodex
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use
Dosage and administration details: Prefilled syringe of 5 ml (250 mg of fulvestrant) : Two slow, intramuscular injections (2 x 250 mg) by month with an additional 500 mg dose two weeks after the initial dose. 5 ml in each buttock with prefilled syringes.	

Number of subjects in period 1	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib
Started	104	100	87
Completed	9	3	1
Not completed	95	97	86
Patient's choice	1	3	2
Adverse event, non-fatal	8	9	3
Death	3	3	5

Other	7	5	3
Intercurrent disease	-	-	-
Complication	-	1	-
Second cancer	-	1	-
Lack of efficacy	76	75	73

Number of subjects in period 1	B2 - EGFR WT Erlotinib Fulvestrant
Started	88
Completed	0
Not completed	88
Patient's choice	-
Adverse event, non-fatal	2
Death	4
Other	4
Intercurrent disease	1
Complication	-
Second cancer	-
Lack of efficacy	77

Baseline characteristics

Reporting groups	
Reporting group title	A1 - EGFR mut Gefitinib
Reporting group description:	
EGFR mutated patients receiving Gefitinib.	
Reporting group title	B1 - EGFR mut Gefitinib Fulvestrant
Reporting group description:	
EGFR mutated patients receiving Gefitinib + Fulvestrant	
Reporting group title	A2 - EGFR WT Erlotinib
Reporting group description:	
EGFR WT patients receiving Erlotinib.	
Reporting group title	B2 - EGFR WT Erlotinib Fulvestrant
Reporting group description:	
EGFR WT patients receiving Erlotinib + Fulvestrant	

Reporting group values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib
Number of subjects	104	100	87
Age categorical			
Age distribution			
Units: Subjects			
Adults (18-64 years)	34	38	47
From 65-84 years	69	58	39
85 years and over	1	4	1
Age continuous			
Units: years			
median	67.71	68.30	64.56
full range (min-max)	49.5 to 89.1	50.1 to 90.9	43.6 to 85.4
Gender categorical			
Units: Subjects			
Female	104	100	87
Smoking population			
Number of smoking and non smoking patients			
Units: Subjects			
Smoker	24	31	62
Non smoker	80	69	25
ECOG Performance Status			
Patient's ECOG PS during the screening/inclusion visit.			
Units: Subjects			
ECOG 0	42	42	27
ECOG 1	53	49	46
ECOG 2	9	9	14
Histology subtype			
Histology subtype of patients' cancer			
Units: Subjects			
Adenocarcinoma	99	95	82
Non adenocarcinoma	5	5	5
EGFR mutation			

Patient with an EGFR mutation and patients with a WT EGFR gene.			
Units: Subjects			
EGFR WT	0	0	85
EGFR muted	104	100	0
MISSING			2
Previous line of treatment			
Number of patients' previous line of treatment.			
Units: Subjects			
1 previous line of treatment	104	100	61
2 or more previous lines of treatment	0	0	26
Menopausal status			
Menopausal status of the patients			
Units: Subjects			
Premenopausal patient	0	0	0
Postmenopausal patient	104	100	87
Estrogen Receptor Alpha (ERa)			
Results of the Estrogen Receptor Alpha positivity test			
Units: Subjects			
Negative	34	41	26
Positive	10	9	7
Unknown	60	50	54
Pack-years for smokers			
Number of pack-years for the smokers.			
Units: Pack-years			
median	12	11.5	37.5
full range (min-max)	1 to 54	1 to 50	1 to 92

Reporting group values	B2 - EGFR WT Erlotinib Fulvestrant	Total	
Number of subjects	88	379	
Age categorical			
Age distribution			
Units: Subjects			
Adults (18-64 years)	58	177	
From 65-84 years	30	196	
85 years and over	0	6	
Age continuous			
Units: years			
median	61.03		
full range (min-max)	43.7 to 80.5	-	
Gender categorical			
Units: Subjects			
Female	88	379	
Smoking population			
Number of smoking and non smoking patients			
Units: Subjects			
Smoker	70	187	
Non smoker	18	192	
ECOG Performance Status			
Patient's ECOG PS during the screening/inclusion visit.			
Units: Subjects			

ECOG 0	41	152	
ECOG 1	33	181	
ECOG 2	14	46	
Histology subtype			
Histology subtype of patients' cancer			
Units: Subjects			
Adenocarcinoma	82	358	
Non adenocarcinoma	6	21	
EGFR mutation			
Patient with an EGFR mutation and patients with a WT EGFR gene.			
Units: Subjects			
EGFR WT	88	173	
EGFR muted	0	204	
MISSING		2	
Previous line of treatment			
Number of patients' previous line of treatment.			
Units: Subjects			
1 previous line of treatment	59	324	
2 or more previous lines of treatment	29	55	
Menopausal status			
Menopausal status of the patients			
Units: Subjects			
Premenopausal patient	0	0	
Postmenopausal patient	88	379	
Estrogen Receptor Alpha (ERa)			
Results of the Estrogen Receptor Alpha positivity test			
Units: Subjects			
Negative	25	126	
Positive	8	34	
Unknown	55	219	
Pack-years for smokers			
Number of pack-years for the smokers.			
Units: Pack-years			
median	35		
full range (min-max)	1 to 120	-	

Subject analysis sets

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

Subject analysis set description:

All patients who were included are counted into this subject analysis set

Reporting group values	Intent-to-treat		
Number of subjects	379		
Age categorical			
Age distribution			
Units: Subjects			
Adults (18-64 years)	177		
From 65-84 years	196		

85 years and over	6		

Age continuous			
Units: years			
median	66.18		
full range (min-max)	43.6 to 90.9		
Gender categorical			
Units: Subjects			
Female	379		
Smoking population			
Number of smoking and non smoking patients			
Units: Subjects			
Smoker	187		
Non smoker	192		
ECOG Performance Status			
Patient's ECOG PS during the screening/inclusion visit.			
Units: Subjects			
ECOG 0	152		
ECOG 1	181		
ECOG 2	46		
Histology subtype			
Histology subtype of patients' cancer			
Units: Subjects			
Adenocarcinoma	358		
Non adenocarcinoma	21		
EGFR mutation			
Patient with an EGFR mutation and patients with a WT EGFR gene.			
Units: Subjects			
EGFR WT	173		
EGFR muted	204		
MISSING	2		
Previous line of treatment			
Number of patients' previous line of treatment.			
Units: Subjects			
1 previous line of treatment	324		
2 or more previous lines of treatment	55		
Menopausal status			
Menopausal status of the patients			
Units: Subjects			
Premenopausal patient	0		
Postmenopausal patient	379		
Estrogen Receptor Alpha (ERa)			
Results of the Estrogen Receptor Alpha positivity test			
Units: Subjects			
Negative	126		
Positive	34		
Unknown	219		

Pack-years for smokers			
Number of pack-years for the smokers.			
Units: Pack-years			
median	29		
full range (min-max)	1 to 120		

End points

End points reporting groups

Reporting group title	A1 - EGFR mut Gefitinib
Reporting group description:	
EGFR mutated patients receiving Gefitinib.	
Reporting group title	B1 - EGFR mut Gefitinib Fulvestrant
Reporting group description:	
EGFR mutated patients receiving Gefitinib + Fulvestrant	
Reporting group title	A2 - EGFR WT Erlotinib
Reporting group description:	
EGFR WT patients receiving Erlotinib.	
Reporting group title	B2 - EGFR WT Erlotinib Fulvestrant
Reporting group description:	
EGFR WT patients receiving Erlotinib + Fulvestrant	
Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who were included are counted into this subject analysis set	

Primary: Progression free survival at 9 months

End point title	Progression free survival at 9 months[1]
End point description:	
Progression free survival (PFS) at 9 months for EGFR mutated patients. PFS : The length of time between randomisation and tumour progression or death (any cause).	
End point type	Primary
End point timeframe:	
From inclusion to 9 months post inclusion.	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point : Progression free survival at 9 month is specific to 2 arms (A1 and B1).

End point values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93[2]	93[3]		
Units: Patients				
Number of patient without progression at 9 months	50	54		

Notes:

[2] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[3] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

Statistical analysis title	Progression free survival at 9 month

Statistical analysis description:

EGFR mutated patients:
The statistical hypotheses in mutated patients are as follows:
H0: p0 (9-month progression-free survival rate) ≤ 45%
H1: p1 (9-month progression-free survival rate) ≥ 60%

Under these assumptions, 102 patients (93 + 10% non-evaluable) are needed in each arm, i.e. 204 patients.

Comparison groups	A1 - EGFR mut Gefitinib v B1 - EGFR mut Gefitinib Fulvestrant
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.05
Method	Binomial test
Parameter estimate	Difference of proportion

Notes:

[4] - No comment

Primary: Progression free survival at 3 months

End point title	Progression free survival at 3 months[5]

End point description:

Progression free survival at 3 months for EGFR wild type patients.
PFS : The length of time between randomisation and tumour progression or death (any cause).

End point type	Primary

End point timeframe:

From inclusion to 3 months post inclusion

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point : Progression free survival at 9 month is specific to 2 arms (A2 and B2).

End point values	A2 - EGFR WT Erlotinib	B2 - EGFR WT Erlotinib Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[6]	86[7]		
Units: Patients				
Number of patients without progression at 3 months	29	29		

Notes:

[6] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[7] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

Statistical analysis title	Progression free survival at 3 month

Statistical analysis description:

EGFR-unmutated patients :
The statistical hypotheses in non-mutated patients are as follows:
H0: p0 (Progression-free survival rate at 3 months) ≤ 30%
H1: p1 (3-month progression-free survival rate) ≥ 45%
Under these assumptions, 95 patients (86 + 10% non-evaluable) are needed in each arm, i.e. 190 patients.

Comparison groups	A2 - EGFR WT Erlotinib v B2 - EGFR WT Erlotinib Fulvestrant
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.05
Method	Binomial test
Parameter estimate	Difference of proportion

Notes:
[8] - No comment

Secondary: Response at 2 months at intent to treat population

End point title	Response at 2 months at intent to treat population

End point description:
Response at 2 months at intent to treat population

End point type	Secondary

End point timeframe:
From inclusion to 2 months post inclusion

End point values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib	B2 - EGFR WT Erlotinib Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	100	87	88
Units: Patients				
Complete response	1	0	0	0
Partial response	56	52	3	2
Stable disease	35	34	25	24
Disease progression	12	14	59	62

Statistical analyses

No statistical analyses for this end point

Secondary: Best response in intent to treat population

End point title	Best response in intent to treat population

End point description:
Best response in intent to treat population

End point type	Secondary

End point timeframe:
From inclusion to the end of treatment

End point values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib	B2 - EGFR WT Erlotinib Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	100	87	88
Units: Patients				
Complete response	1	2	1	0
Partial response	71	62	3	3
Stable disease	23	23	26	24
Disease progression	9	13	57	61

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression free survival.
PFS : The length of time between randomisation and tumour progression or death (any cause).

End point type	Secondary

End point timeframe:

From inclusion to the first observed progression (RECIST 1.1)

End point values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib	B2 - EGFR WT Erlotinib Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[9]	93[10]	83[11]	86[12]
Units: month				
median (confidence interval 95%)				
PFS	9.4 (8.0 to 12.7)	9.9 (7.7 to 11.2)	2.0 (1.8 to 2.6)	1.8 (1.7 to 2.1)

Notes:

[9] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[10] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[11] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

[12] - Intent to treat patients restricted to the number of necessary subjects calculated in the protocole

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (in months)

End point type	Secondary

End point timeframe:

From inclusion to death.

End point values	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib	B2 - EGFR WT Erlotinib Fulvestrant
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	98	83	88
Units: month				
median (confidence interval 95%)				
Overall survival in months	29.9 (23.2 to 43.8)	22.1 (18.6 to 25.7)	7.3 (5.4 to 9.3)	10.0 (6.6 to 14.6)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring was performed at day 15 of the first cycle, before each cycle (i.e., every 4 weeks until the end of protocol treatment), and for 30 days after drug discontinuation for each patient

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	A1 - EGFR mut Gefitinib

Reporting group description:

Patients with an EGFR mutation who received gefitinib only

Reporting group title	B1 - EGFR mut Gefitinib Fulvestrant

Reporting group description:

Patients with an EGFR mutation who received gefitinib anf fulvestrant

Reporting group title	A2 - EGFR WT Erlotinib

Reporting group description:

Patients with a WT EGFR who received erlotinib only

Reporting group title	B2 - EGFR WT Erlotinib Fulvestrant

Reporting group description:

Patients with a WT EGFR who received erlotinib and fulvestrant

Serious adverse events	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 103 (32.04%)	26 / 99 (26.26%)	46 / 87 (52.87%)
number of deaths (all causes)	3	3	7
number of deaths resulting from adverse events	0	1	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	0 / 103 (0.00%)	2 / 99 (2.02%)	5 / 87 (5.75%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 3
Colon cancer stage 0			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Metastases to meninges			

subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pericarditis malignant			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Second primary malignancy			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis superficial			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Pulmonary embolism			
subjects affected / exposed	5 / 103 (4.85%)	2 / 99 (2.02%)	3 / 87 (3.45%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Superior vena cava syndrome			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombophlebitis superficial			

subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous thrombosis limb			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest pain			
subjects affected / exposed	1 / 103 (0.97%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
General physical health deterioration			
subjects affected / exposed	4 / 103 (3.88%)	5 / 99 (5.05%)	16 / 87 (18.39%)
occurrences causally related to treatment / all	1 / 4	1 / 6	2 / 17
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 12
Inflammation			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Malaise			

subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Medical device pain			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Pyrexia			
subjects affected / exposed	2 / 103 (1.94%)	0 / 99 (0.00%)	0 / 87 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Cough			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Dyspnoea			

subjects affected / exposed	3 / 103 (2.91%)	1 / 99 (1.01%)	4 / 87 (4.60%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 103 (0.97%)	1 / 99 (1.01%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 103 (1.94%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Respiratory distress			
subjects affected / exposed	2 / 103 (1.94%)	1 / 99 (1.01%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory failure			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	1 / 103 (0.97%)	1 / 99 (1.01%)	0 / 87 (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
Mania			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Suicidal ideation			
subjects affected / exposed	0 / 103 (0.00%)	2 / 99 (2.02%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Weight decreased			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Injury, poisoning and procedural complications			

Accident at home			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Fall			
subjects affected / exposed	4 / 103 (3.88%)	1 / 99 (1.01%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Humerus fracture			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Wrist fracture			
subjects affected / exposed	1 / 103 (0.97%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia supraventricular			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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

Atrial fibrillation			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
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 tamponade			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Pericardial effusion			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Tachycardia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Nervous system disorders			
Balance disorder			
subjects affected / exposed	2 / 103 (1.94%)	0 / 99 (0.00%)	0 / 87 (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
Brain oedema			
subjects affected / exposed	0 / 103 (0.00%)	2 / 99 (2.02%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebrovascular accident			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Cognitive disorder			

subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Hemiplegia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hypoaesthesia oral			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Hypokinesia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
IIIrd nerve disorder			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorder			
subjects affected / exposed	1 / 103 (0.97%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Paraesthesia			

subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Visual acuity reduced			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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

Diarrhoea			
subjects affected / exposed	2 / 103 (1.94%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Gastrointestinal obstruction			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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 obstruction			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Nausea			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Stomatitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic failure			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Hepatocellular injury			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Jaundice			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	0 / 87 (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
Subacute cutaneous lupus erythematosus			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal colic			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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			
Back pain			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 103 (1.94%)	2 / 99 (2.02%)	3 / 87 (3.45%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter site infection			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium colitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Cystitis			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infectious pleural effusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 99 (1.01%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Spinal cord infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	0 / 87 (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
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 103 (0.00%)	0 / 99 (0.00%)	1 / 87 (1.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 103 (0.00%)	2 / 99 (2.02%)	2 / 87 (2.30%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Serious adverse events	B2 - EGFR WT Erlotinib Fulvestrant		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 88 (37.50%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	4		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial carcinoma			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon cancer stage 0			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastases to meninges			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericarditis malignant			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Second primary malignancy			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			

subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phlebitis superficial				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Superior vena cava syndrome				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis superficial				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Venous thrombosis limb				
subjects affected / exposed	0 / 88 (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 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gait disturbance				
subjects affected / exposed	0 / 88 (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	12 / 88 (13.64%)			
occurrences causally related to treatment / all	1 / 13			
deaths causally related to treatment / all	0 / 7			
Inflammation				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Medical device pain				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				

subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	0 / 88 (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	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cough				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 88 (5.68%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Haemoptysis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				

subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicidal ideation				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				

Alanine aminotransferase increased				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Weight decreased				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Accident at home				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fall				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fracture				

subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wrist fracture				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Arrhythmia supraventricular				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pericardial effusion				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tachycardia				

subjects affected / exposed	0 / 88 (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	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral haemorrhage			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cognitive disorder			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiplegia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoaesthesia oral			

subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokinesia				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
IIIrd nerve disorder				
subjects affected / exposed	0 / 88 (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 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neuralgia				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Partial seizures				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 88 (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 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Dysphagia			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Proctitis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	5 / 88 (5.68%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 2			
Hepatobiliary disorders				
Cholestasis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatocellular injury				

subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Jaundice				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Rash				
subjects affected / exposed	1 / 88 (1.14%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subacute cutaneous lupus erythematosus				
subjects affected / exposed	0 / 88 (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	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone pain				

subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Infections and infestations				
Anal abscess				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	2 / 88 (2.27%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Catheter site infection				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium colitis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ophthalmic herpes simplex				
subjects affected / exposed	0 / 88 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vaginal infection			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	A1 - EGFR mut Gefitinib	B1 - EGFR mut Gefitinib Fulvestrant	A2 - EGFR WT Erlotinib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 103 (98.06%)	99 / 99 (100.00%)	87 / 87 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	3 / 103 (2.91%)	11 / 99 (11.11%)	0 / 87 (0.00%)
occurrences (all)	12	56	0

Epistaxis			
subjects affected / exposed	7 / 103 (6.80%)	7 / 99 (7.07%)	2 / 87 (2.30%)
occurrences (all)	12	9	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	45 / 103 (43.69%)	56 / 99 (56.57%)	34 / 87 (39.08%)
occurrences (all)	117	131	82
Chest pain			
subjects affected / exposed	16 / 103 (15.53%)	12 / 99 (12.12%)	10 / 87 (11.49%)
occurrences (all)	48	28	18
General physical health deterioration			
subjects affected / exposed	7 / 103 (6.80%)	9 / 99 (9.09%)	19 / 87 (21.84%)
occurrences (all)	8	10	25
Fatigue			
subjects affected / exposed	7 / 103 (6.80%)	11 / 99 (11.11%)	13 / 87 (14.94%)
occurrences (all)	12	25	18
Oedema peripheral			
subjects affected / exposed	8 / 103 (7.77%)	10 / 99 (10.10%)	7 / 87 (8.05%)
occurrences (all)	13	27	7
Xerosis			
subjects affected / exposed	11 / 103 (10.68%)	6 / 99 (6.06%)	2 / 87 (2.30%)
occurrences (all)	20	26	3
Pain			
subjects affected / exposed	4 / 103 (3.88%)	5 / 99 (5.05%)	6 / 87 (6.90%)
occurrences (all)	6	10	7
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	32 / 103 (31.07%)	33 / 99 (33.33%)	20 / 87 (22.99%)
occurrences (all)	109	74	42
Dyspnoea			
subjects affected / exposed	34 / 103 (33.01%)	25 / 99 (25.25%)	27 / 87 (31.03%)
occurrences (all)	88	77	57
Chest pain			
subjects affected / exposed	12 / 103 (11.65%)	10 / 99 (10.10%)	3 / 87 (3.45%)
occurrences (all)	24	13	3
Productive cough			

subjects affected / exposed	6 / 103 (5.83%)	2 / 99 (2.02%)	4 / 87 (4.60%)
occurrences (all)	10	3	4
Psychiatric disorders			
Depression			
subjects affected / exposed	6 / 103 (5.83%)	6 / 99 (6.06%)	1 / 87 (1.15%)
occurrences (all)	21	7	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	35 / 103 (33.98%)	29 / 99 (29.29%)	7 / 87 (8.05%)
occurrences (all)	115	104	12
Aspartate aminotransferase increased			
subjects affected / exposed	29 / 103 (28.16%)	25 / 99 (25.25%)	9 / 87 (10.34%)
occurrences (all)	110	102	18
Gamma-glutamyltransferase increased			
subjects affected / exposed	13 / 103 (12.62%)	15 / 99 (15.15%)	10 / 87 (11.49%)
occurrences (all)	45	49	18
Weight decreased			
subjects affected / exposed	7 / 103 (6.80%)	14 / 99 (14.14%)	17 / 87 (19.54%)
occurrences (all)	16	18	21
Blood alkaline phosphatase increased			
subjects affected / exposed	15 / 103 (14.56%)	10 / 99 (10.10%)	6 / 87 (6.90%)
occurrences (all)	42	23	10
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 103 (13.59%)	7 / 99 (7.07%)	4 / 87 (4.60%)
occurrences (all)	26	17	9
Paraesthesia			
subjects affected / exposed	6 / 103 (5.83%)	7 / 99 (7.07%)	3 / 87 (3.45%)
occurrences (all)	15	9	38
Dysgeusia			
subjects affected / exposed	3 / 103 (2.91%)	6 / 99 (6.06%)	2 / 87 (2.30%)
occurrences (all)	3	7	3
Confusional state			
subjects affected / exposed	0 / 103 (0.00%)	5 / 99 (5.05%)	0 / 87 (0.00%)
occurrences (all)	0	6	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	14 / 103 (13.59%)	20 / 99 (20.20%)	31 / 87 (35.63%)
occurrences (all)	62	51	50
Neutropenia			
subjects affected / exposed	8 / 103 (7.77%)	4 / 99 (4.04%)	3 / 87 (3.45%)
occurrences (all)	44	14	3
Thrombocytopenia			
subjects affected / exposed	4 / 103 (3.88%)	4 / 99 (4.04%)	6 / 87 (6.90%)
occurrences (all)	6	18	8
Lymphopenia			
subjects affected / exposed	5 / 103 (4.85%)	4 / 99 (4.04%)	6 / 87 (6.90%)
occurrences (all)	13	8	10
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	7 / 103 (6.80%)	9 / 99 (9.09%)	3 / 87 (3.45%)
occurrences (all)	13	14	3
Eye disorders			
Dry eye			
subjects affected / exposed	8 / 103 (7.77%)	7 / 99 (7.07%)	8 / 87 (9.20%)
occurrences (all)	18	16	10
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	66 / 103 (64.08%)	60 / 99 (60.61%)	42 / 87 (48.28%)
occurrences (all)	338	287	95
Nausea			
subjects affected / exposed	21 / 103 (20.39%)	25 / 99 (25.25%)	24 / 87 (27.59%)
occurrences (all)	41	62	34
Vomiting			
subjects affected / exposed	14 / 103 (13.59%)	10 / 99 (10.10%)	17 / 87 (19.54%)
occurrences (all)	19	12	20
Constipation			
subjects affected / exposed	17 / 103 (16.50%)	13 / 99 (13.13%)	6 / 87 (6.90%)
occurrences (all)	34	25	6
Stomatitis			
subjects affected / exposed	12 / 103 (11.65%)	6 / 99 (6.06%)	10 / 87 (11.49%)
occurrences (all)	18	11	16
Abdominal pain			

subjects affected / exposed	12 / 103 (11.65%)	8 / 99 (8.08%)	6 / 87 (6.90%)
occurrences (all)	17	11	8
Abdominal pain upper			
subjects affected / exposed	12 / 103 (11.65%)	10 / 99 (10.10%)	3 / 87 (3.45%)
occurrences (all)	17	19	3
Dry mouth			
subjects affected / exposed	6 / 103 (5.83%)	10 / 99 (10.10%)	5 / 87 (5.75%)
occurrences (all)	6	12	6
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 103 (8.74%)	4 / 99 (4.04%)	1 / 87 (1.15%)
occurrences (all)	25	10	2
Aphthous stomatitis			
subjects affected / exposed	6 / 103 (5.83%)	2 / 99 (2.02%)	1 / 87 (1.15%)
occurrences (all)	13	3	1
Pyrexia			
subjects affected / exposed	10 / 103 (9.71%)	3 / 99 (3.03%)	1 / 87 (1.15%)
occurrences (all)	11	3	1
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	50 / 103 (48.54%)	43 / 99 (43.43%)	18 / 87 (20.69%)
occurrences (all)	221	158	54
Rash			
subjects affected / exposed	36 / 103 (34.95%)	31 / 99 (31.31%)	20 / 87 (22.99%)
occurrences (all)	99	91	37
Acne			
subjects affected / exposed	11 / 103 (10.68%)	13 / 99 (13.13%)	15 / 87 (17.24%)
occurrences (all)	30	34	25
Erythema			
subjects affected / exposed	18 / 103 (17.48%)	16 / 99 (16.16%)	5 / 87 (5.75%)
occurrences (all)	33	30	13
Pruritus			
subjects affected / exposed	17 / 103 (16.50%)	14 / 99 (14.14%)	7 / 87 (8.05%)
occurrences (all)	35	30	8
Skin fissures			
subjects affected / exposed	10 / 103 (9.71%)	10 / 99 (10.10%)	4 / 87 (4.60%)
occurrences (all)	43	17	10

Skin toxicity			
subjects affected / exposed	12 / 103 (11.65%)	6 / 99 (6.06%)	4 / 87 (4.60%)
occurrences (all)	23	9	5
Nail disorder			
subjects affected / exposed	14 / 103 (13.59%)	8 / 99 (8.08%)	1 / 87 (1.15%)
occurrences (all)	27	16	3
Alopecia			
subjects affected / exposed	9 / 103 (8.74%)	11 / 99 (11.11%)	1 / 87 (1.15%)
occurrences (all)	17	29	2
Dermatitis acneiform			
subjects affected / exposed	5 / 103 (4.85%)	5 / 99 (5.05%)	5 / 87 (5.75%)
occurrences (all)	11	7	27
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	10 / 103 (9.71%)	7 / 99 (7.07%)	12 / 87 (13.79%)
occurrences (all)	35	32	46
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	21 / 103 (20.39%)	17 / 99 (17.17%)	9 / 87 (10.34%)
occurrences (all)	57	42	15
Arthralgia			
subjects affected / exposed	12 / 103 (11.65%)	18 / 99 (18.18%)	8 / 87 (9.20%)
occurrences (all)	20	38	11
Bone pain			
subjects affected / exposed	9 / 103 (8.74%)	10 / 99 (10.10%)	8 / 87 (9.20%)
occurrences (all)	18	17	19
Musculoskeletal pain			
subjects affected / exposed	5 / 103 (4.85%)	9 / 99 (9.09%)	5 / 87 (5.75%)
occurrences (all)	7	13	5
Muscle spasms			
subjects affected / exposed	11 / 103 (10.68%)	9 / 99 (9.09%)	2 / 87 (2.30%)
occurrences (all)	28	40	7
Pain in extremity			
subjects affected / exposed	7 / 103 (6.80%)	7 / 99 (7.07%)	1 / 87 (1.15%)
occurrences (all)	10	13	2
Myalgia			

subjects affected / exposed	6 / 103 (5.83%)	3 / 99 (3.03%)	3 / 87 (3.45%)
occurrences (all)	6	4	4
Musculoskeletal chest pain			
subjects affected / exposed	1 / 103 (0.97%)	6 / 99 (6.06%)	0 / 87 (0.00%)
occurrences (all)	1	7	0
Infections and infestations			
Folliculitis			
subjects affected / exposed	10 / 103 (9.71%)	12 / 99 (12.12%)	8 / 87 (9.20%)
occurrences (all)	61	40	18
Paronychia			
subjects affected / exposed	15 / 103 (14.56%)	10 / 99 (10.10%)	3 / 87 (3.45%)
occurrences (all)	45	26	17
Bronchitis			
subjects affected / exposed	8 / 103 (7.77%)	8 / 99 (8.08%)	5 / 87 (5.75%)
occurrences (all)	15	9	6
Urinary tract infection			
subjects affected / exposed	7 / 103 (6.80%)	9 / 99 (9.09%)	3 / 87 (3.45%)
occurrences (all)	13	18	3
Conjunctivitis			
subjects affected / exposed	8 / 103 (7.77%)	8 / 99 (8.08%)	2 / 87 (2.30%)
occurrences (all)	25	19	3
Rhinitis			
subjects affected / exposed	6 / 103 (5.83%)	8 / 99 (8.08%)	3 / 87 (3.45%)
occurrences (all)	12	13	4
Cystitis			
subjects affected / exposed	7 / 103 (6.80%)	5 / 99 (5.05%)	1 / 87 (1.15%)
occurrences (all)	10	8	1
Nasopharyngitis			
subjects affected / exposed	6 / 103 (5.83%)	5 / 99 (5.05%)	1 / 87 (1.15%)
occurrences (all)	6	5	1
Lung infection			
subjects affected / exposed	1 / 103 (0.97%)	0 / 99 (0.00%)	5 / 87 (5.75%)
occurrences (all)	1	0	6
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	20 / 103 (19.42%)	26 / 99 (26.26%)	34 / 87 (39.08%)
occurrences (all)	38	52	54
Hypoalbuminaemia			
subjects affected / exposed	5 / 103 (4.85%)	5 / 99 (5.05%)	6 / 87 (6.90%)
occurrences (all)	10	12	10

Non-serious adverse events	B2 - EGFR WT Erlotinib Fulvestrant		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 88 (97.73%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	11		
Epistaxis			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	5		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	25 / 88 (28.41%)		
occurrences (all)	41		
Chest pain			
subjects affected / exposed	10 / 88 (11.36%)		
occurrences (all)	13		
General physical health deterioration			
subjects affected / exposed	13 / 88 (14.77%)		
occurrences (all)	15		
Fatigue			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	4		
Xerosis			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	6		
Pain			

subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	28 / 88 (31.82%)		
occurrences (all)	44		
Dyspnoea			
subjects affected / exposed	23 / 88 (26.14%)		
occurrences (all)	36		
Chest pain			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Psychiatric disorders			
Depression			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	11		
Aspartate aminotransferase increased			
subjects affected / exposed	12 / 88 (13.64%)		
occurrences (all)	19		
Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 88 (15.91%)		
occurrences (all)	20		
Weight decreased			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	7		
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 88 (13.64%)		
occurrences (all)	17		

Nervous system disorders			
Headache			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	5		
Paraesthesia			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Dysgeusia			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Confusional state			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	29 / 88 (32.95%)		
occurrences (all)	48		
Neutropenia			
subjects affected / exposed	6 / 88 (6.82%)		
occurrences (all)	16		
Thrombocytopenia			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	14		
Lymphopenia			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	8		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Eye disorders			
Dry eye			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			

subjects affected / exposed	42 / 88 (47.73%)		
occurrences (all)	101		
Nausea			
subjects affected / exposed	23 / 88 (26.14%)		
occurrences (all)	32		
Vomiting			
subjects affected / exposed	17 / 88 (19.32%)		
occurrences (all)	20		
Constipation			
subjects affected / exposed	9 / 88 (10.23%)		
occurrences (all)	13		
Stomatitis			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	4		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	7		
Aphthous stomatitis			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	22 / 88 (25.00%)		
occurrences (all)	42		

Rash subjects affected / exposed occurrences (all)	28 / 88 (31.82%) 64		
Acne subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 13		
Erythema subjects affected / exposed occurrences (all)	6 / 88 (6.82%) 8		
Pruritus subjects affected / exposed occurrences (all)	5 / 88 (5.68%) 5		
Skin fissures subjects affected / exposed occurrences (all)	5 / 88 (5.68%) 13		
Skin toxicity subjects affected / exposed occurrences (all)	6 / 88 (6.82%) 6		
Nail disorder subjects affected / exposed occurrences (all)	2 / 88 (2.27%) 2		
Alopecia subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1		
Dermatitis acneiform subjects affected / exposed occurrences (all)	2 / 88 (2.27%) 4		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	8 / 88 (9.09%) 13		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	7 / 88 (7.95%) 13		
Arthralgia			

subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	6		
Bone pain			
subjects affected / exposed	10 / 88 (11.36%)		
occurrences (all)	18		
Musculoskeletal pain			
subjects affected / exposed	7 / 88 (7.95%)		
occurrences (all)	7		
Muscle spasms			
subjects affected / exposed	1 / 88 (1.14%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	5 / 88 (5.68%)		
occurrences (all)	9		
Myalgia			
subjects affected / exposed	0 / 88 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 88 (2.27%)		
occurrences (all)	2		
Infections and infestations			
Folliculitis			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	5		
Paronychia			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	6		
Bronchitis			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	4 / 88 (4.55%)		
occurrences (all)	5		
Conjunctivitis			
subjects affected / exposed	3 / 88 (3.41%)		
occurrences (all)	5		

Rhinitis subjects affected / exposed occurrences (all) Cystitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Lung infection subjects affected / exposed occurrences (all)	1 / 88 (1.14%) 1 1 / 88 (1.14%) 1 0 / 88 (0.00%) 0 4 / 88 (4.55%) 4		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	22 / 88 (25.00%) 30 4 / 88 (4.55%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2012	This amendment concerns the addition of 10% additional patients in order to take into account patients who will not be evaluable, the clarification of the inclusion criteria, the addition of the actions to be taken according to the toxicities of gefitinib, the addition of side effects of fulvestrant and various corrections in particular in the statistical part.
10 December 2012	This amendment concerns: - the addition of new investigation centers - the removal of three centres: Lille Oscar Lambret, Maubeuge polyclinic and Saint-Omer - the change of address of one center (Toulon CHI) - the elimination of the realization of the partial pressure of oxygen at inclusion - the removal of the QLQ-C30 questionnaire - minor protocol fixes.
07 May 2015	This amendment concerns: - extension of the study - the change of investigator for five centres: Le Mans CHG, Dax, Reims CHU, Clamart, Bobigny - the addition in the protocol of a maximum delay in the start of treatment - clarification of the non-inclusion criterion for patients who have already received an experimental drug. - modification of the non-inclusion criterion on anticoagulants - the addition of an additional ancillary study

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32144133