



Clinical trial results:

Phase II study evaluating the combination of cetuximab with afatinib as first-line treatment for patients with EGFR mutated Non Small Cell Lung Cancer

Summary

EudraCT number	2015-003390-15
Trial protocol	FR
Global end of trial date	30 May 2020

Results information

Result version number	v1 (current)
This version publication date	03 June 2022
First version publication date	03 June 2022

Trial information

Trial identification

Sponsor protocol code	IFCT-1503
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02716311
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 156811045, contact@ifct.fr
Scientific contact	Contact, 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 August 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluating efficacy and toxicity of the combination of afatinib with cetuximab versus afatinib alone, in first-line treatment of patient with a EGFR mutated NSCLC

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	16 June 2016
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: 117
Worldwide total number of subjects	117
EEA total number of subjects	117

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)	55
From 65 to 84 years	61
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 117 of 172 (68%) patients initially planned had been included in the study between June 2016 and November 2018 and randomly assigned to group afatinib (59) or group afatinib + cetuximab (58). Only one patient (group afatinib + cetuximab) did not receive any study treatment due to the presence of intercurrent disease.

Pre-assignment

Screening details:

patients with stage III/IV EGFR-positive NSCLC

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	A - Afatinib

Arm description:

Afatinib alone

Arm type	Active comparator
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib will be taken orally from D1 and until progression or dose-limiting toxicity, at the dose of 40 mg/d.

Arm title	B - Afatinib + cetuximab
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Arm description:

Afatinib in combinaison with cetuximab

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib will be taken orally from D1 and until progression or dose-limiting toxicity, at the dose of 40 mg/d.

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

Dosage and administration details:

Cetuximab will be administered by intravenous infusion from D15 of the 1st cycle (C1D15) at the dose of 250 mg/m² then every 2 weeks at the dose of 500 mg/m², for 6 months.

Number of subjects in period 1	A - Afatinib	B - Afatinib + cetuximab
Started	59	58
Completed	0	0
Not completed	59	58
Patient's choice	-	1
Treatment not started	-	1
Adverse event, non-fatal	6	9
Death	1	1
Other	7	4
Intercurrent disease	-	1
2nd cancer	1	-
Lack of efficacy	44	41

Baseline characteristics

Reporting groups

Reporting group title	A - Afatinib
Reporting group description: Afatinib alone	
Reporting group title	B - Afatinib + cetuximab
Reporting group description: Afatinib in combinaison with cetuximab	

Reporting group values	A - Afatinib	B - Afatinib + cetuximab	Total
Number of subjects	59	58	117
Age categorical Units: Subjects			
Adults (18-64 years)	22	33	55
From 65-84 years	36	25	61
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	65.63	63.61	
standard deviation	± 11.49	± 10.69	-
Gender categorical Units: Subjects			
Female	43	41	84
Male	16	17	33
Smoking history Units: Subjects			
No	35	32	67
Yes	24	26	50
EGFR mutation type Units: Subjects			
Deletion exon 19	33	32	65
Mutation G719X exon 18	2	0	2
Mutation L858R exon 21	23	24	47
Mutation L861Q	1	2	3
ECOG performance status Units: Subjects			
PS = 0	21	21	42
PS = 1	38	36	74
PS = 2	0	1	1
TNM stage Units: Subjects			
IIIa	1	0	1
IIIb	0	3	3
IVa	17	13	30
IVb	41	42	83
Brain metastases Units: Subjects			

No	44	46	90
Yes	15	12	27
Histologic type Units: Subjects			
Adenocarcinoma (unspecified)	57	56	113
Non-small cell non-squamous cancer	1	1	2
Mixed carcinoma	1	1	2
Smoking history Units: Pack, years			
median	20	16	
full range (min-max)	2 to 112	1 to 60	-

End points

End points reporting groups

Reporting group title	A - Afatinib
Reporting group description:	
Afatinib alone	
Reporting group title	B - Afatinib + cetuximab
Reporting group description:	
Afatinib in combinaison with cetuximab	
Subject analysis set title	Efficacy population
Subject analysis set type	Per protocol
Subject analysis set description:	
Efficacy population is defined as all patient without major deviation on inclusion or exclusion criteria.	

Primary: Treatment failure-free survival (TTF) at 9 months

End point title	Treatment failure-free survival (TTF) at 9 months ^[1]
End point description:	
Treatment failure was defined as treatment discontinuation for any reason (including disease progression, death, or toxicity).	
End point type	Primary
End point timeframe:	
9 months after randomization	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Non comparative study

End point values	A - Afatinib	B - Afatinib + cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57 ^[2]		
Units: percent				
number (confidence interval 95%)	59.27 (45.66 to 70.55)	64.91 (51.06 to 75.74)		

Notes:

[2] - Efficacy population analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Median TTF

End point title	Median TTF
End point description:	
End point type	Secondary
End point timeframe:	
Until the end of the study (median follow-up time of 21.7 months)	

End point values	A - Afatinib	B - Afatinib + cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57 ^[3]		
Units: month				
median (confidence interval 95%)	11.1 (8.48 to 14.13)	12.94 (9.20 to 14.52)		

Notes:

[3] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival

End point title	Median Progression Free Survival
End point description: Progression-free survival is defined as the time between randomisation and tumour progression or death by any cause.	
End point type	Secondary
End point timeframe: Until the end of the study (median follow-up time of 21.7 months)	

End point values	A - Afatinib	B - Afatinib + cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57 ^[4]		
Units: month				
median (confidence interval 95%)	11.89 (9.10 to 15.01)	13.44 (9.66 to 13.80)		

Notes:

[4] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate
End point description: Patients are assessable for response after two cycles. The response will be assessed by planimetric measurement of unidimensional targets according to RECIST criteria (version 1.1 Eur J Cancer 2009;45:228-247) at each assessment.	
End point type	Secondary
End point timeframe: Until the end of the study (median follow-up of 21.7 months)	

End point values	A - Afatinib	B - Afatinib + cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57 ^[5]		
Units: percent				
number (not applicable)	42	37		

Notes:

[5] - Efficacy population

Statistical analyses

No statistical analyses for this end point

Secondary: 12-month survival rate

End point title	12-month survival rate
End point description:	
Overall survival is defined as the time from date of enrolment and death by all causes.	
End point type	Secondary
End point timeframe:	
12 months after randomization	

End point values	A - Afatinib	B - Afatinib + cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent				
number (confidence interval 95%)	87.92 (76.31 to 94.05)	89.4 (77.92 to 95.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any adverse event occurring from the signature of consent up to 30 days after the end of administration.

Adverse event reporting additional description:

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

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21
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Reporting groups

Reporting group title	Safety Population - Arm A - Afatinib
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Reporting group description:

Safety population is defined as all patients who received a dose of treatment.

Reporting group title	Safety Population - Arm B - Afatinib + cetuximab
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Reporting group description: -

Serious adverse events	Safety Population - Arm A - Afatinib	Safety Population - Arm B - Afatinib + cetuximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 59 (37.29%)	56 / 57 (98.25%)	
number of deaths (all causes)	32	31	
number of deaths resulting from adverse events	2	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			
subjects affected / exposed	2 / 59 (3.39%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Phlebitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	3 / 59 (5.08%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia malignant			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac tamponade			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericarditis			
subjects affected / exposed	1 / 59 (1.69%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Retinal detachment			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	6 / 59 (10.17%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	4 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	7 / 59 (11.86%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	4 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			

subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash papular			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 59 (3.39%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes simplex			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Folliculitis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 59 (1.69%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Safety Population - Arm A - Afatinib	Safety Population - Arm B - Afatinib + cetuximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 59 (6.78%)	2 / 57 (3.51%)	
occurrences (all)	6	8	
Pulmonary embolism			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 59 (33.90%)	32 / 57 (56.14%)	
occurrences (all)	64	111	
Mucosal inflammation			
subjects affected / exposed	13 / 59 (22.03%)	19 / 57 (33.33%)	
occurrences (all)	45	42	
Chest pain			
subjects affected / exposed	9 / 59 (15.25%)	14 / 57 (24.56%)	
occurrences (all)	19	37	
Fatigue			
subjects affected / exposed	6 / 59 (10.17%)	12 / 57 (21.05%)	
occurrences (all)	19	23	
Oedema peripheral			

subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 6	6 / 57 (10.53%) 10	
Xerosis subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 7	6 / 57 (10.53%) 8	
Pain subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	5 / 57 (8.77%) 9	
Pyrexia subjects affected / exposed occurrences (all)	6 / 59 (10.17%) 6	2 / 57 (3.51%) 2	
General physical health deterioration subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 6	1 / 57 (1.75%) 2	
Chest discomfort subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	3 / 57 (5.26%) 3	
Reproductive system and breast disorders Vulvovaginal dryness subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	2 / 57 (3.51%) 2	
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	15 / 59 (25.42%) 47	24 / 57 (42.11%) 49	
Epistaxis subjects affected / exposed occurrences (all)	11 / 59 (18.64%) 23	14 / 57 (24.56%) 38	
Dyspnoea exertional subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	9 / 57 (15.79%) 15	
Lung disorder subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 6	3 / 57 (5.26%) 8	
Rhinorrhoea			

subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 7	4 / 57 (7.02%) 6	
Productive cough subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 5	3 / 57 (5.26%) 5	
Dysphonia subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 3	3 / 57 (5.26%) 4	
Haemoptysis subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 3	3 / 57 (5.26%) 4	
Nasal dryness subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 4	1 / 57 (1.75%) 2	
Pleural effusion subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	3 / 57 (5.26%) 3	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 2	4 / 57 (7.02%) 16	
Anxiety subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 2	5 / 57 (8.77%) 5	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	8 / 59 (13.56%) 29	13 / 57 (22.81%) 21	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 14	8 / 57 (14.04%) 16	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 12	7 / 57 (12.28%) 16	
Blood bilirubin increased			

subjects affected / exposed	3 / 59 (5.08%)	2 / 57 (3.51%)	
occurrences (all)	9	16	
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 59 (5.08%)	6 / 57 (10.53%)	
occurrences (all)	4	19	
Weight decreased			
subjects affected / exposed	9 / 59 (15.25%)	9 / 57 (15.79%)	
occurrences (all)	14	9	
Blood magnesium decreased			
subjects affected / exposed	3 / 59 (5.08%)	4 / 57 (7.02%)	
occurrences (all)	5	16	
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 59 (5.08%)	4 / 57 (7.02%)	
occurrences (all)	6	7	
Neutrophil count decreased			
subjects affected / exposed	1 / 59 (1.69%)	5 / 57 (8.77%)	
occurrences (all)	1	8	
Transaminases increased			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 59 (8.47%)	11 / 57 (19.30%)	
occurrences (all)	19	17	
Neuralgia			
subjects affected / exposed	2 / 59 (3.39%)	3 / 57 (5.26%)	
occurrences (all)	14	4	
Dysgeusia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 57 (5.26%)	
occurrences (all)	9	3	
Sciatica			
subjects affected / exposed	2 / 59 (3.39%)	3 / 57 (5.26%)	
occurrences (all)	2	8	
Paraesthesia			

subjects affected / exposed occurrences (all)	2 / 59 (3.39%) 3	3 / 57 (5.26%) 5	
Hypoaesthesia subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	3 / 57 (5.26%) 5	
Neuropathy peripheral subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 1	3 / 57 (5.26%) 3	
Presyncope subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 3	0 / 57 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	13 / 59 (22.03%) 38	7 / 57 (12.28%) 25	
Lymphopenia subjects affected / exposed occurrences (all)	4 / 59 (6.78%) 8	9 / 57 (15.79%) 31	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 59 (1.69%) 2	6 / 57 (10.53%) 10	
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	7 / 59 (11.86%) 14	10 / 57 (17.54%) 20	
Dry eye subjects affected / exposed occurrences (all)	5 / 59 (8.47%) 12	9 / 57 (15.79%) 16	
Keratitis subjects affected / exposed occurrences (all)	3 / 59 (5.08%) 13	2 / 57 (3.51%) 4	
Trichomegaly subjects affected / exposed occurrences (all)	0 / 59 (0.00%) 0	3 / 57 (5.26%) 8	
Eye pain			

subjects affected / exposed	1 / 59 (1.69%)	3 / 57 (5.26%)	
occurrences (all)	1	5	
Visual impairment			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	6	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	56 / 59 (94.92%)	52 / 57 (91.23%)	
occurrences (all)	338	271	
Stomatitis			
subjects affected / exposed	18 / 59 (30.51%)	17 / 57 (29.82%)	
occurrences (all)	46	36	
Nausea			
subjects affected / exposed	20 / 59 (33.90%)	17 / 57 (29.82%)	
occurrences (all)	41	32	
Constipation			
subjects affected / exposed	4 / 59 (6.78%)	15 / 57 (26.32%)	
occurrences (all)	15	25	
Vomiting			
subjects affected / exposed	12 / 59 (20.34%)	13 / 57 (22.81%)	
occurrences (all)	19	20	
Abdominal pain			
subjects affected / exposed	8 / 59 (13.56%)	9 / 57 (15.79%)	
occurrences (all)	16	14	
Abdominal pain upper			
subjects affected / exposed	5 / 59 (8.47%)	7 / 57 (12.28%)	
occurrences (all)	5	15	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 59 (10.17%)	5 / 57 (8.77%)	
occurrences (all)	10	10	
Dry mouth			
subjects affected / exposed	4 / 59 (6.78%)	5 / 57 (8.77%)	
occurrences (all)	9	9	
Dysphagia			
subjects affected / exposed	3 / 59 (5.08%)	3 / 57 (5.26%)	
occurrences (all)	15	3	

Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	47 / 59 (79.66%)	54 / 57 (94.74%)	
occurrences (all)	288	437	
Nail disorder			
subjects affected / exposed	31 / 59 (52.54%)	35 / 57 (61.40%)	
occurrences (all)	172	224	
Skin fissures			
subjects affected / exposed	23 / 59 (38.98%)	32 / 57 (56.14%)	
occurrences (all)	76	185	
Hypertrichosis			
subjects affected / exposed	4 / 59 (6.78%)	14 / 57 (24.56%)	
occurrences (all)	12	44	
Pruritus			
subjects affected / exposed	6 / 59 (10.17%)	15 / 57 (26.32%)	
occurrences (all)	14	37	
Alopecia			
subjects affected / exposed	11 / 59 (18.64%)	4 / 57 (7.02%)	
occurrences (all)	34	7	
Skin toxicity			
subjects affected / exposed	6 / 59 (10.17%)	7 / 57 (12.28%)	
occurrences (all)	7	10	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 59 (3.39%)	5 / 57 (8.77%)	
occurrences (all)	2	6	
Hair texture abnormal			
subjects affected / exposed	1 / 59 (1.69%)	3 / 57 (5.26%)	
occurrences (all)	1	4	
Skin burning sensation			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Eczema			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	3	
Dry skin			

subjects affected / exposed occurrences (all)	21 / 59 (35.59%) 70	35 / 57 (61.40%) 141	
Renal and urinary disorders			
Cough			
subjects affected / exposed	22 / 59 (37.29%)	26 / 57 (45.61%)	
occurrences (all)	37	57	
Renal failure			
subjects affected / exposed	6 / 59 (10.17%)	3 / 57 (5.26%)	
occurrences (all)	14	25	
Haematuria			
subjects affected / exposed	0 / 59 (0.00%)	3 / 57 (5.26%)	
occurrences (all)	0	5	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 59 (16.95%)	14 / 57 (24.56%)	
occurrences (all)	21	31	
Arthralgia			
subjects affected / exposed	12 / 59 (20.34%)	7 / 57 (12.28%)	
occurrences (all)	28	16	
Bone pain			
subjects affected / exposed	6 / 59 (10.17%)	6 / 57 (10.53%)	
occurrences (all)	11	15	
Neck pain			
subjects affected / exposed	4 / 59 (6.78%)	4 / 57 (7.02%)	
occurrences (all)	20	6	
Muscle spasms			
subjects affected / exposed	8 / 59 (13.56%)	4 / 57 (7.02%)	
occurrences (all)	16	5	
Pain in extremity			
subjects affected / exposed	3 / 59 (5.08%)	5 / 57 (8.77%)	
occurrences (all)	7	10	
Musculoskeletal chest pain			
subjects affected / exposed	4 / 59 (6.78%)	3 / 57 (5.26%)	
occurrences (all)	11	5	
Myalgia			

subjects affected / exposed	4 / 59 (6.78%)	2 / 57 (3.51%)	
occurrences (all)	11	5	
Musculoskeletal pain			
subjects affected / exposed	3 / 59 (5.08%)	3 / 57 (5.26%)	
occurrences (all)	7	3	
Infections and infestations			
Cystitis			
subjects affected / exposed	4 / 59 (6.78%)	3 / 57 (5.26%)	
occurrences (all)	7	4	
Nasopharyngitis			
subjects affected / exposed	5 / 59 (8.47%)	5 / 57 (8.77%)	
occurrences (all)	5	6	
Rhinitis			
subjects affected / exposed	4 / 59 (6.78%)	3 / 57 (5.26%)	
occurrences (all)	5	5	
Urinary tract infection			
subjects affected / exposed	4 / 59 (6.78%)	4 / 57 (7.02%)	
occurrences (all)	4	5	
Angular cheilitis			
subjects affected / exposed	3 / 59 (5.08%)	2 / 57 (3.51%)	
occurrences (all)	10	6	
Oral herpes			
subjects affected / exposed	3 / 59 (5.08%)	0 / 57 (0.00%)	
occurrences (all)	3	0	
Bronchitis			
subjects affected / exposed	2 / 59 (3.39%)	3 / 57 (5.26%)	
occurrences (all)	3	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 59 (22.03%)	16 / 57 (28.07%)	
occurrences (all)	19	25	
Hypokalaemia			
subjects affected / exposed	10 / 59 (16.95%)	4 / 57 (7.02%)	
occurrences (all)	16	6	
Hypoalbuminaemia			

subjects affected / exposed	4 / 59 (6.78%)	3 / 57 (5.26%)	
occurrences (all)	4	7	
Hypocalcaemia			
subjects affected / exposed	2 / 59 (3.39%)	3 / 57 (5.26%)	
occurrences (all)	3	8	
Hyponatraemia			
subjects affected / exposed	3 / 59 (5.08%)	1 / 57 (1.75%)	
occurrences (all)	4	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2016	The 1st amendment aimed to clarify the assessments to be made during the study, the dose reductions, to add an additional blood tube for a total volume of 20 mL and to modify the patient information letter following the review of the patient committee of the Ligue contre le Cancer.
29 August 2018	The 3rd amendment aimed to Add an interim analysis Make various corrections to the protocol and synopsis Declare the new version of the afatinib SmPC. This modification did not have an impact on patient safety but have an impact on the expected or unexpected nature of serious adverse events. To modify the patient information consent letter following the update of the afatinib SmPC and in order to bring it into compliance with the European Data Protection Regulation. Translated with www.DeepL.com/Translator (free version)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported