



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 |
|-----------------------|-----------|

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 |
|------------------|--------------------------|

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 |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 21 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Safety Population - Arm A - Afatinib |
|-----------------------|--------------------------------------|

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 |
|-----------------------|--|

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 | 5 / 59 (8.47%) | 4 / 57 (7.02%) | |
| occurrences (all) | 7 | 6 | |
| Productive cough | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 3 / 57 (5.26%) | |
| occurrences (all) | 5 | 5 | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 3 / 57 (5.26%) | |
| occurrences (all) | 3 | 4 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 3 / 57 (5.26%) | |
| occurrences (all) | 3 | 4 | |
| Nasal dryness | | | |
| subjects affected / exposed | 3 / 59 (5.08%) | 1 / 57 (1.75%) | |
| occurrences (all) | 4 | 2 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 59 (0.00%) | 3 / 57 (5.26%) | |
| occurrences (all) | 0 | 3 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 59 (1.69%) | 4 / 57 (7.02%) | |
| occurrences (all) | 2 | 16 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 59 (3.39%) | 5 / 57 (8.77%) | |
| occurrences (all) | 2 | 5 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 8 / 59 (13.56%) | 13 / 57 (22.81%) | |
| occurrences (all) | 29 | 21 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 7 / 59 (11.86%) | 8 / 57 (14.04%) | |
| occurrences (all) | 14 | 16 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 4 / 59 (6.78%) | 7 / 57 (12.28%) | |
| occurrences (all) | 12 | 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 occurrences (all) | 1 / 59 (1.69%) 1 | 3 / 57 (5.26%) 5 | |
| Visual impairment subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 6 | 0 / 57 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 56 / 59 (94.92%) 338 | 52 / 57 (91.23%) 271 | |
| Stomatitis subjects affected / exposed occurrences (all) | 18 / 59 (30.51%) 46 | 17 / 57 (29.82%) 36 | |
| Nausea subjects affected / exposed occurrences (all) | 20 / 59 (33.90%) 41 | 17 / 57 (29.82%) 32 | |
| Constipation subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 15 | 15 / 57 (26.32%) 25 | |
| Vomiting subjects affected / exposed occurrences (all) | 12 / 59 (20.34%) 19 | 13 / 57 (22.81%) 20 | |
| Abdominal pain subjects affected / exposed occurrences (all) | 8 / 59 (13.56%) 16 | 9 / 57 (15.79%) 14 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 59 (8.47%) 5 | 7 / 57 (12.28%) 15 | |
| Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) | 6 / 59 (10.17%) 10 | 5 / 57 (8.77%) 10 | |
| Dry mouth subjects affected / exposed occurrences (all) | 4 / 59 (6.78%) 9 | 5 / 57 (8.77%) 9 | |
| Dysphagia subjects affected / exposed occurrences (all) | 3 / 59 (5.08%) 15 | 3 / 57 (5.26%) 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 | <p>The 3rd amendment aimed to</p> <p>Add an interim analysis</p> <p>Make various corrections to the protocol and synopsis</p> <p>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.</p> <p>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.</p> <p>Translated with www.DeepL.com/Translator (free version)</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported