IFCT-1003 LADIE Trial: Randomized phase II trial evaluating treatment with EGFR-TKI versus EGFR-TKI associated with anti-estrogen (fulvestrant) in women with non-squamous advanced stage NSCLC.

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Sponsored by the French Cooperative Thoracic Intergroup (IFCT) – 75009 PARIS (France)

BACKGROUND

- The incidence of lung cancer is increasing dramatically in women and displays some specific epidemiological, radiological, clinical and pathological characteristics.
- Two main mechanisms emerged from recent findings in the field of lung carcinogenesis in women: the preferential involvement of the EGFR pathway and the potential impact of hormonal factors.
- The interaction of estrogen receptors with growth factor receptor signalling has also been shown.
- Preclinical data have shown that the combination of an EGFR-Tyrosine Kinase Inhibitor (TKI) with an anti-estrogen could overcome resistance to EGFR-TKI.

OBJECTIVE

- **Primary objective**
  - Progression-free survival at 3 months and 9 months for EGFR WT (wild-type) patients and EGFR-mutated patients respectively.
- **Secondary objectives**
  - Combined toxicity of EGFR-TKI and fulvestrant (NCI-CTCAE 4.0)
  - Response rate (RECIST 1.1)
  - Overall survival
  - Quality of life (LCSS)
- **Exploratory objectives**
  - To identify prognostic and response predictive serum and tissue biomarkers.

STATISTICAL METHODS

Randomized Phase II study (Fleming one-stage method),
with a 5% unilateral alpha risk, and a power of 90% in each of the 4 arms.

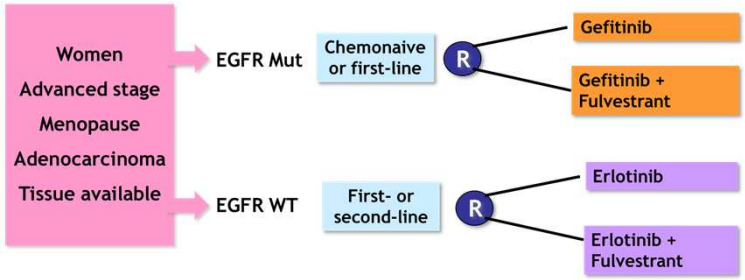
- ***Patients without EGFR mutations:***

H0: p0 (Progression-free survival at three months) ≤ 30%
H1: p1 (Progression-free survival at three months) ≥ 50%
Based on these hypotheses, 86 patients are needed in each arm.
Nine additional patients in each arm will be included to take into account 10% of non evaluable patients. A total of **190 patients** is so needed.

- ***Patients with EGFR mutations:***

H0: p0 (Progression-free survival at nine months) ≤ 45%
H1: p1 (Progression-free survival at nine months) ≥ 60%
Based on these hypotheses, 93 patients are needed in each arm.
Nine additional patients in each arm will be included to take into account 10% of non evaluable patients. A total of **204 patients** is so needed.

TRIAL DESIGN



- Biological and clinical follow-ups are performed in both arms every month to minimize the potential bias due to monthly fulvestrant injection.
- Tumor assessment is performed every 8 weeks in both arms until progression

TREATMENTS

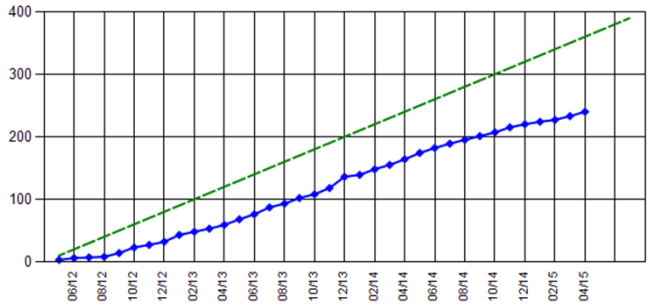
- **EGFR mutated group :** Patients are treated by gefitinib (250 mg/d) vs. gefitinib + fulvestrant 500 mg MI / month (with a supplementary dose at day 15) in first- or second-line setting
- **EGFR wild-type group** : Patients are treated by erlotinib (150 mg/d) vs. erlotinib + fulvestrant 500 mg MI / month (with a supplementary dose at day 15) in the in second- or third-line setting.
- Treatments are given until progression or unacceptable toxicity.

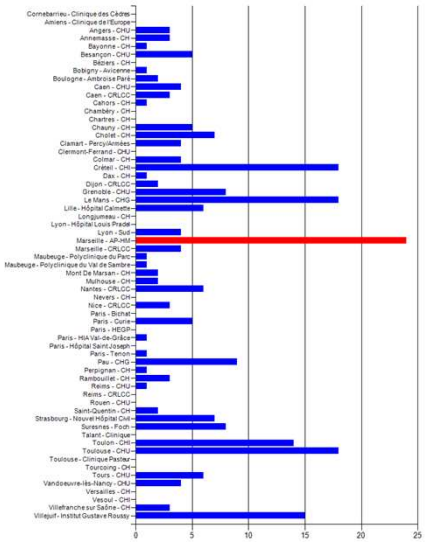
ELIGIBILITY CRITERIA

- Histologically-confirmed non-squamous NSCLC
- Not suitable for radiation, inoperable stage III or stage IV
- Presence of at least one lesion that can be measured by CT scan (RECIST v1.1)
- Available tumor tissue for EGFR mutation analysis
- Post-menopausal women
- PS 0-2
- For EGFR mutated patients: chemonaive or one line of previous chemotherapy
- For EGFR WT patients: one or two previous lines of chemotherapy

ACCRUAL (21/05/2015)

240 patients (100 EGFR+ 140 EGFR WT) from 44 French centers included. The end of accrual can be expected for September 2016.





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