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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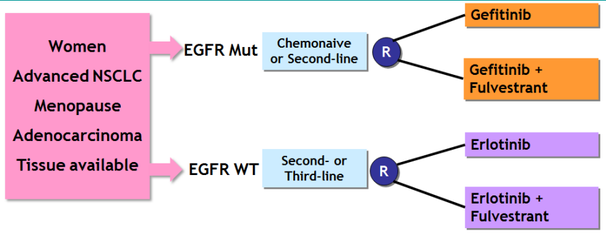
BACKGROUND

- 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.
  To detect T790M mutation in circulating DNA of EGFR-mutated patient
  To correlate circulating DNA with clinical outcome

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

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 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 needed.

TREATMENTS

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

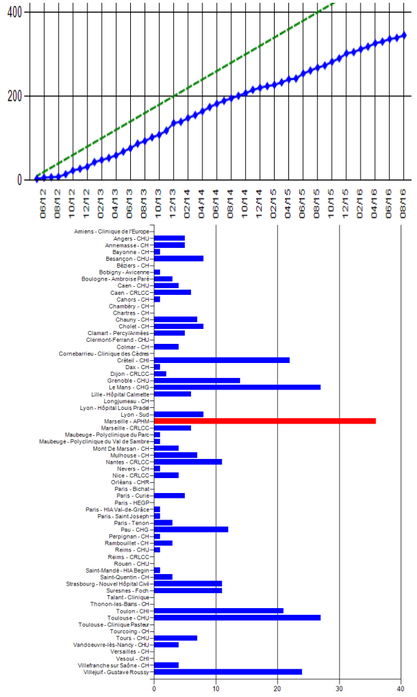
ELIGIBILITY CRITERIA

- 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
  - No EGFR TK mutation reported to confer resistance to EGFR TKI : i.e., exon 20 mutation (T790M or S768IEGFR) or exon 20 insertion
- For EGFR WT patients: one or two previous lines of chemotherapy

ACCRUAL (12/09/2016)

348 patients (179 EGFR MUT and 169 EGFR WT) from 47 French centres
The end of accrual can be expected for March 2017

25 patients EGFR mutated were analysed for T790M mutation (study started in July 2015).



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