TIMELY: Multicentre phase II trial of first-line afatinib in patients with suspected/confirmed EGFR mutant NSCLC - ctDNA & long-term efficacy

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Background

- Efficacy of afatinib in epidermal growth factor receptor (EGFR) mutant patients with comorbidities or those with suspected EGFR mutations unfit for chemotherapy is poorly explored.
- We evaluated afatinib in this population, with serial plasma circulating tumour DNA (ctDNA) to investigate the role of molecular EGFR genotyping and monitoring.

Methods

- A phase-II trial, which enrolled NSCLC patients with comorbidities precluding chemotherapy, and either:

  (i) EGFR-mutation, PS 0-3, or

  (ii) Suspected EGFR-mutation (tissue unavailable/failed genotyping)

  - never/former-light smoker,
  - adenocarcinoma, and
  - WHO performance status 0-2

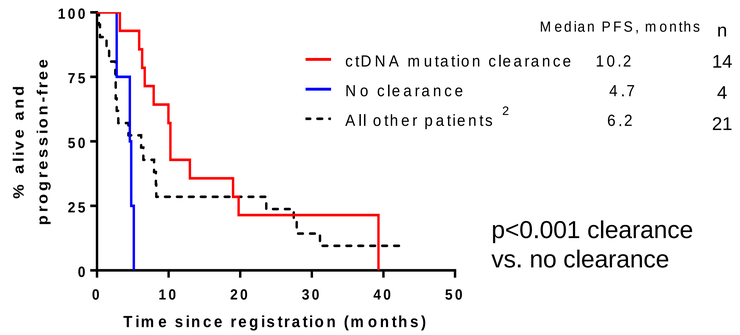
- Afatinib (40mg daily) given until progression/toxicity.
- Blood samples obtained at baseline and 12-weekly until discontinuation.
- **Plasma ctDNA measured using InVisionSeq™ - Lung (amplicon-based next-generation sequencing).**

EGFR Patient Groups

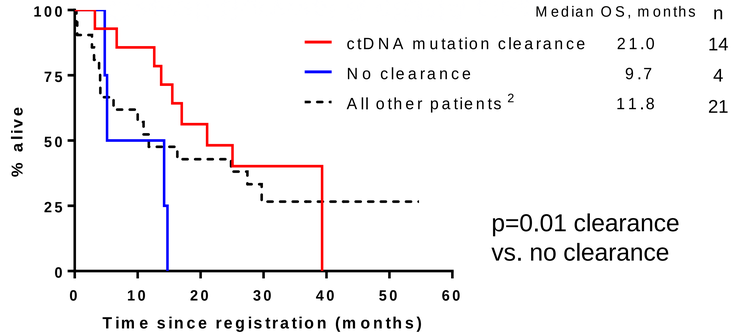
- **39 patients** recruited (14 UK centres).
- Median age **72 years.**
- Upon trial entry:
  - **27** patients had **PS 0-1**
  - **12** patients had **PS 2-3**
  - **21 patients** (54%) had **known tissue EGFR-mutations**
- Overall, **74%** (29/39) **of patients were EGFR-mutant;** ctDNA confirmed 8 additional patients who had unknown EGFR status at baseline (8/17;47%).

Results

Progression-Free Survival & ctDNA clearance[1]



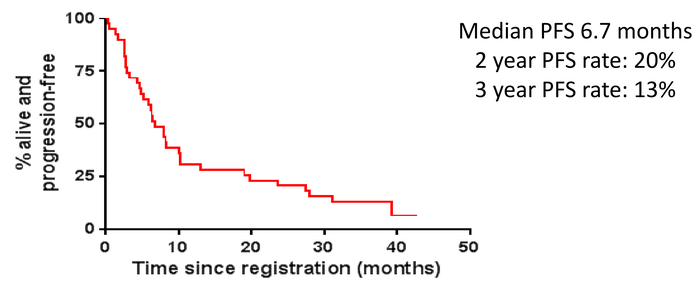
Overall Survival & ctDNA clearance



[1] baseline ctDNA values became undetectable during serial measurements

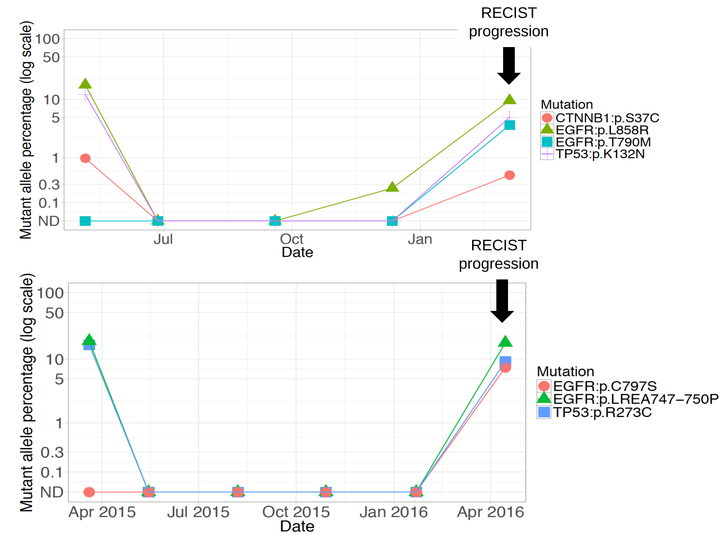
[2] six cases without serial ctDNA measurements and 15 without mutations

Progression-Free Survival



Resistance and Progression

- In April 2018, 5/39 patients survived >36 months, including 4/39 progression-free (median follow-up 33 months, maximum 55).
- 40% (4/10) of mutant cases who discontinued after 3 cycles due to progressive disease developed an exon 20 EGFR-mutation.
- Combined tissue and ctDNA data identified 21 patients with common mutations (exon 19/L858R) and 8 with rare mutations (exon 18/20). 10 patients remain suspected.
- Corresponding median PFS of these cohorts were 10.2/3.9/5.3 months, with 6-month PFS of 71/38/50% all exceeding the 30% target; median OS were 24.8/5.7/11.4 months (p<0.001). Therefore, all patient groups benefitted; known EGFR-mutants having best outcomes.



Conclusions

- Patients unsuitable for chemotherapy with confirmed/suspected EGFR-mutations by tissue or ctDNA **benefit** from afatinib.
- **Serial ctDNA** has **potential** as a **useful biomarker** for stratification and monitoring; amplicon-based ctDNA analysis can identify EGFR mutations when tissue is unavailable.
- **ctDNA clearance** during afatinib treatment is **strongly associated** with **better PFS/OS.**
- **Exon 20 mutations** were observed at **acquired resistance**.

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