Background

- Efficacy of afatinib in epidermal growth factor receptor (EGFR) mutant patients with comorbidities or those with suspected EGFR mutations until 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:
  1. EGFR-mutation, PS 0-3, or
  2. 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

- Median PFS 6.7 months
- 2 year PFS rate: 20%
- 3 year PFS rate: 13%

Overall Survival & ctDNA clearance

- Median OS, months
- ctDNA mutation clearance 21.0
- No clearance 9.7
- All other patients 11.8

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 19/885R) 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.