# Clinical utility of ctDNA for detection of *EGFR, ALK, BRAFV600E* alterations and resistance mutations in patients with NSCLC at failure to targeted therapy

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## Background

- The comprehensive genomic profile by next generation sequencing (NGS) of circulating tumour DNA (ctDNA) can identify a wide spectrum of genomic alterations (GAs) in non-small cell lung cancer (NSCLC)
- At progression disease, liquid biopsy (LB) offers a non-invasive and easy-to-obtain alternative to tissue profiling considered the gold standard
- We aimed to assess the **clinical utility of amplicon-based ctDNA NGS for detecting GAs and resistance mutations at progressive disease** (PD) in advanced NSCLC patients (pts)

## Methods

- **Prospective plasma sample collection** in pts with advanced NSCLC harboring *EGFR* mutations (m), *ALK* rearrangements (r) and *BRAF*m at tyrosine-kinase inhibitors (TKI) failure between Nov/2015 and May/2019 at Gustave Roussy (GR)
- LB was collected at PD and analyzed using InVisionFirst®-Lung
- The detection rate of driver and resistance GAs on ctDNA were evaluated
- For assessing resistance in the *EGFR*m/*ALK*r population, clinically informative results were defined as ≥1 resistance mutations at TKI failure

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M. Riudavets declares no conflicts of interest.

## Results

### Patient's characteristics

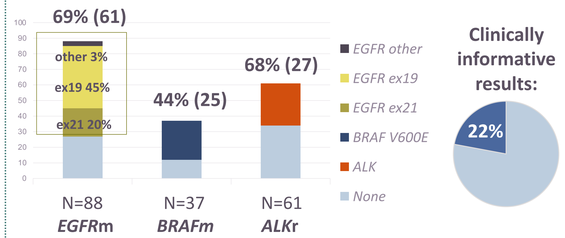
- A total of **222 samples** were collected from 134 pts with NSCLC harboring GAs:
  - 58 pts with *EGFR*m
  - 12 pts with *BRAF*m
  - 36 pts with *ALK*r
  - 28 pts with other GAs
- Median number of samples per patient was 1 [range 1-8]

| Clinical characteristics | | N=134 (%) |
|---|---|---|
| **Age**, median [range] | | 62 [24-92] |
| **Gender** | male<br>female | 56 (42)<br>78 (58) |
| **Smoking status** | non- or light smokers*<br>smokers<br>missing | 70 (54)<br>60 (46)<br>4 |
| **Histology** | squamous<br>non-squamous | 2 (1)<br>132 (99) |
| **Stage at diagnosis** | IA-IIB<br>IIIA-IIIB<br>IVA-IVB | 3 (2)<br>15 (11)<br>116 (87) |
| **Number of treatment lines** [range] | | 3 [1-11] |
| **Metastatic sites at LB** | ≤2<br>>2 | 53 (40)<br>81 (60) |

*light smokers = less than 15 packs of cigarettes per year

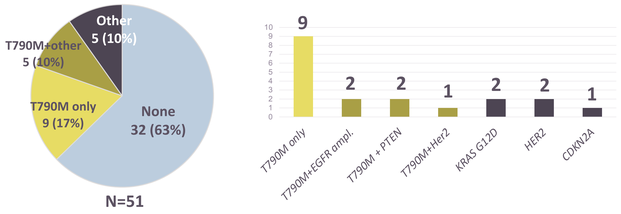
### Driver genomic alterations: ctDNA detection rate

- Driver GAs at disease progression were the following:

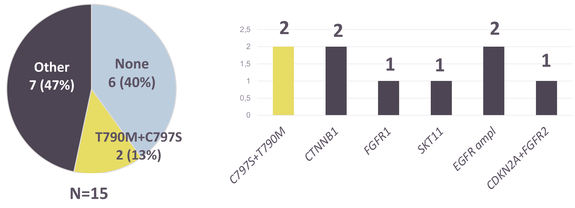



### *EGFR* ex19/21 resistance mutations: ctDNA detection rate

- After 1st/2nd gen. TKI, the ***T790M*** was detected in 27% (14/51) of samples

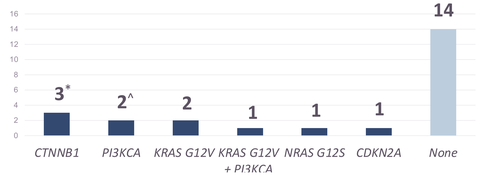



- After osimertinib (given in all cases as ≥2 line), the ***C797S*** rate was 13% (2/15)




### *BRAF V600E* resistance mutations: ctDNA detection rate

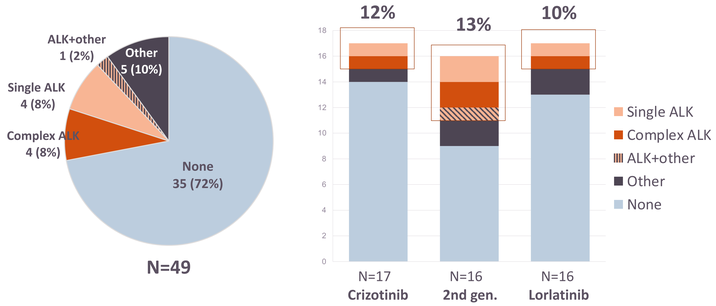
- In samples from ***BRAF*m** pts treated with TKI (n=24; 22 with dabrafenib-trametinib), a total of 42% molecular alterations were found at PD:



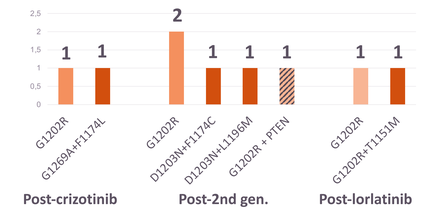

*after dabrafenib; ^after vemurafenib

### *ALK* resistance mutations: ctDNA detection rate

- ***ALK* resistance mutations:**
  - After crizotinib, ≥1 *ALK* resistance mutations were found in 12% (2/17)
  - After 2nd generation TKI (n=16), in 31% (5/16), and after lorlatinib in 13% (2/17)




- ***ALK* resistance mutations by TKI generation:**




- Other molecular alterations were found in 8% of samples: *NRAS G12C* (after crizotinib), *NTRK3* and *PI3KCA* (2nd gen.), and *HER2* and *MET* ampl. (lorlatinib)

## Conclusions

- **ctDNA is feasible in patients with NSCLC harbouring *EGFR*m, *ALK*r, *BRAF*m for detecting driver and resistance genomic alterations at progressive disease**
- ctDNA provides clinical informative results for treatment tailoring at TKI failure
- Liquid biopsy at progression could be useful to select the subsequent therapy