Osimertinib benefit in *ct*DNA *T790M* positive, *EGFR*-mutant NSCLC patients

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BACKGROUND

•The third generation tyrosine kinase inhibitors (TKIs) osimertinib is approved for patients with acquired epidermal growth factor receptor (*EGFR*) *T790M* mutations in advanced non-small cell lung cancer (NSCLC) patients (1,2).
New tissue biopsy to detect T790M cannot always be performed, due to the size or location of the lesions and risk of complications to the patient. As an alternative, liquid biopsies based on circulating cell-free tumor DNA (*ct*DNA) analysis have been described.

OBJECTIVE

•We assessed the efficacy of osimertinib (Response Rate by RECIST 1.1 criteria and Progression-free survival) when T790M status is determined in circulating cell-free tumour DNA (*ct*DNA) from blood samples in progressing advanced *EGFR*-mutant NSCLC patients.
•.We assessed correlation between RECIST radiological responses with osimertinib and three *ct*DNA predictors: (A) *T790M* allele fraction, (B) *EGFR* activating mutation allele fraction, and (C) *T790M* by *EGFR* activating mutation allele fraction ratio was evaluated.

METHODS

•10 ml of blood were collected in EDTA-K2 tubes and processed at the time of disease progression. DNA was extracted from < 5 ml of plasma and analysed using Inivata's enhanced Tam-Seq™.

RESULTS

Clinical Characteristics

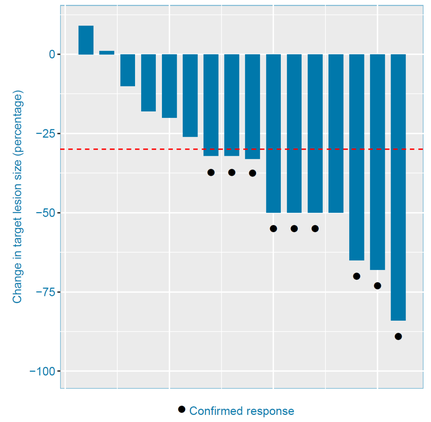
•From April 2015 and April 2016. 48 *EGFR*-mutant advanced NSCLC patients with acquired resistance to EGFR TKIs without a tissue biopsy were recruited in a single center. Main patients' clinical characteristics are reported in Table 1.

	N= 48 (%)
Median age- years (range)	65 y (37-83)
Gender	
-Female	36 (75)
-Male	12 (25)
***EGFR* mutation subtype:**	
-Del19	33 (69)
-L858R	15 (31)
Smoking status:	
-Never smoker	28 (58)
-Former smoker	19 (40)

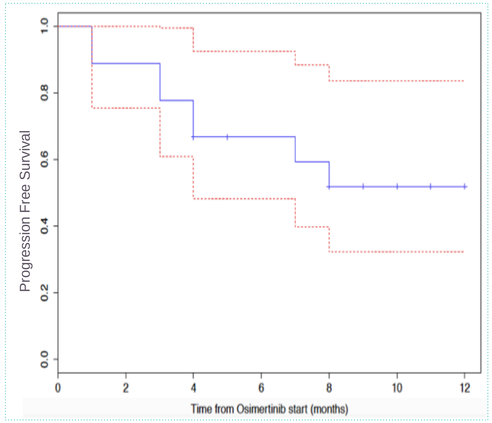
Table1. Patients' characteristics

RESPONSE RATE and PROGRESSION FREE SURVIVAL

Of the 24 NSCLC patients with *T790M* positivity in the *ct*DNA, 18 received osimertinib (80 mg daily) at progression, and 16 were evaluated for response. 65% had received at least 3 previous treatment lines.

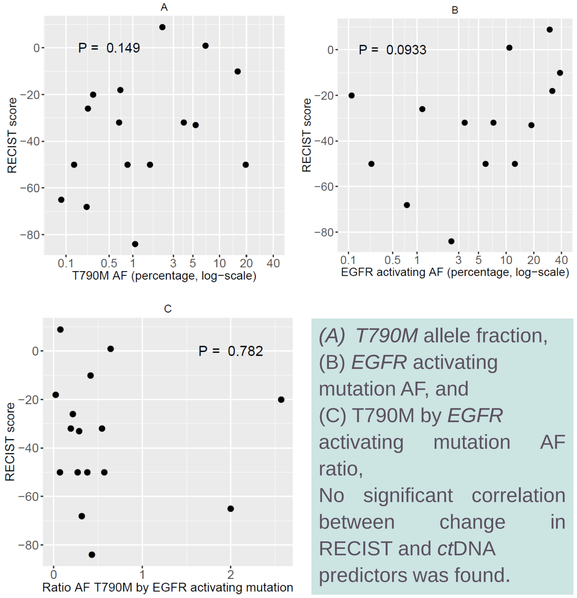


10 had a partial response (62.5%), and 6 had stable disease (37.5%).
90% of patients had confirmed responses.



Median PFS not achieved (95% CI: 4-NA),
6- and 12-months PFS of 66.7% and 52%.
Median follow up of 8.5 months.

RECIST and *ct*DNA predictors



(A) T790M allele fraction,
(B) *EGFR* activating mutation AF, and
(C) T790M by *EGFR* activating mutation AF ratio,
No significant correlation between change in RECIST and *ct*DNA predictors was found.

T790M mutation

•The *T790M* positivity in *ct*DNA was reported in 24 out of 48 (50%) NSCLC patients.
•Among 9 out of the 24 patients with *ct*DNA *T790M*-positivity, the T790M allele fraction (AF) was lower than 0.5% in the liquid biopsy

CONCLUSIONS

- **In *ct*DNA *T790M* mutated NSCLC patients, osimertinib induce a response rate of 62.5% and a 12-months progression free survival of 52% .**
- ***T790M* allele fraction did not predict for response, and good clinical responses were achieved even in patients with *T790M* AF below 0.1%**
- ***ct*DNA from liquid biopsy can be used as a surrogate marker for *T790M* in tumour tissue.**

Bibliography: (1) Jänne – NEJM 2015 * (2) Goss – Lancet Oncol 2016