Ultrasensitive detection of EGFR T790M mutation by droplet digital PCR (ddPCR) in TKI naïve NSCLC harboring *EGFR* mutation: results of the nationwide program Biomarkers France of the French Cooperative Thoracic Intergroup (IFCT)

Charlotte Leduc[1], Erwan Pencreach[2], Jean-Pierre Merlio[3], Pierre-Paul Bringuier[4], F. de Fraipont[5], F. Escande[6], Antoinette Lemoine[7], Ouafik L'Houcine[8], Hélène Blons[9], Marc Denis[10], Paul Hofman[11], Roger Lacave[12], Samia Melaabi[13], Alexandra Langlais[14], Pascale Missy[14], Franck Morin[14], Fabrice Barlesi[15], Denis Moro-Sibilot[16], Jacques Cadranel[17] & Michèle Beau-Faller[2]

[1]Chest Department, CHU Strasbourg, FR ; [2]Laboratory of Biochemistry and Molecular Biology, CHU Strasbourg, FR, [3]Department of Biology and Pathology, CHU Bordeaux, FR, [4]Laboratoire d'Anatomie Pathologique, CHU Lyon, FR, [5]Biochimie des Cancers et Biothérapies, CHU Grenoble, FR, [6]Laboratoire de Biochimie et Biologie moléculaire, CHU Lille, FR, [7]Biochimie et Oncogénétique INSERM UMR-S 1193, Hôpital Paul Brousse -Hôpitaux Universitaires Paris-Sud, Villejuif, FR, [8]Service de Transfert d'Oncologie Biologique, APHM, Marseille, FR, 9Department of biochemistry, Pharmacogenetics and Molecular Oncology, HEGP, FR, [10]Molecular Biology, CHU Nantes, FR, [11]Laboratory of clinical and experimental pathology, CHU Nice, FR, [12]Service d'Histologie, Embryologie, Cytogénétique biologie tumorale et génétique moléculaire, Hopital Tenon, FR, [13]Service de génétique - Unité de Pharmacogénomique, Institut Curie, FR, [14]French Cooperative Thoracic Intergroup, Paris, FR, [15]Multidisciplinary Oncology & Therapeutic Innovations, CHU Marseille, FR, [16]Thoracic oncology, CHU Grenoble , FR, [17]Service de Pneumologie, CHU Tenon, Paris, FR.

BACKGROUND

The presence of EGFR T790M mutation accounts for > 50% of the acquired resistance to EGFR-TKIs. Earlier studies performed in small cohorts suggest that T790M was also detected in TKI-naïve NSCLC, with discordant results.

OBJECTIVE

We use ddPCR to address the incidence/clinical significance of baseline pre-treatment T790M mutation in a large cohort of TKI-naïve NSCLC.

METHODS

We re-analyzed 366 EGFR mutated patients of the IFCT Biomarkers France program (1)(2) with available tumor DNA that were finally treated by EGFR-TKI. ddPCR was performed with QX200 system (BIO-RAD®, Hercules, USA). We used restriction enzyme (Hae III®) to improve ddPCR profiles for FFPE DNA analysis. All samples were tested in duplicate (in two independent wells). A cohort of FFPE colon cancer DNA (n=30) was used as negative controls. Theoretical limit of detection was 0,005% and analytical sensitivity was 0,03%. Discordant replicates and false positive results were excluded.

CONCLUSIONS

Ultrasensitive detection of T790M mutation is related in 9% of *EGFR* mutated TKI naïve NSCLC patients and has a negative prognostic value for T790M mutation FA over 10%, but no impact on EGFR-TKI response. New strategies of therapies assessed could be tested in such populations.

RESULTS

Frequency of pre-treatment T790M mutation: 23/256 (9%)

		T790M - (N=233)	T790M + (N=23)	Total (N=256)	p-value
Sex	Male	69 (29.6)	7 (30.4)	76 (29.7)	0.93
	Female	164 (70.4)	16 (69.6)	180 (70.3)	
Age (years)	Median	69.40	74.81	69.47	0.70
	Range	[30.6-94.0]	[40.7-88.8]	[30.6-94.0]	
Origin	Asian	11 (5.4)	1 (4.8)	12 (4.7)	1.00
	Non Asian	193 (94.6)	20 (95.2)	213 (83.2)	
Smoking status	Smoker	29 (12.7)	2 (9.5)	31 (12.1)	0.13
	Former smoker	64 (27.9)	2 (9.5)	66 (25.8)	
	Non-smoker	136 (59.4)	17 (81.0)	153 (59.8)	
PS	0-1	179 (80.7)	20 (90.9)	199 (77.7)	0.55
	≥ 2	40 (18.3)	2 (9.1)	42 (16.5)	
	MISSING	14	1	15	
Histology	Squamous	2 (0.9)	0	2 (0.8)	0.50
	Adenocarcinoma	200 (85.8)	18 (78.3)	218 (85.2)	
	Large Cell	3 (1.3)	0	3 (1.2)	
	Other	28 (12.0)	5 (21.7)	33 (12.9)	

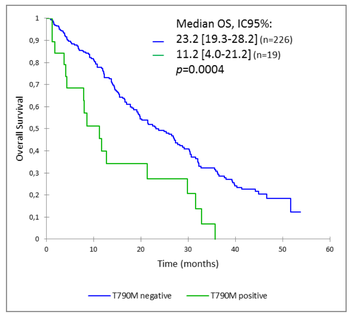
Table 1 : Patients' characteristics (n=256)

T790M status	Slow progression	Classical progression	Rapid progression	p-value
T790M negative	37 (21.3%)	108 (62.1%)	29 (16.7%)	0.02
T790M positive	3 (15.0%)	8 (40.0%)	9 (45.0%)	

FA	Slow progression	Classical progression	Rapid progression	p-value
0	37 (21.3%)	108 (62.1%)	29 (16.7%)	0.007
[0.01%-0.1%[	3 (60.0%)	1 (20.0%)	1 (20.0%)	
[0.1%-1.0%[	0	3 (75.0%)	1 (25.0%)	
[1.0%-10.0%[	0	3 (42.9%)	4 (57.1%)	
≥ 10.0%	0	1 (25.0%)	3 (75.0%)	

Table 2 : Correlation between T790M mutation fractional abundance (FA) and time of progression (n=194)

Slow progression: PFS ≤ 3 months; c Classical progression: PFS 3-20 months; Rapid progression: PFS ≥ 20 months



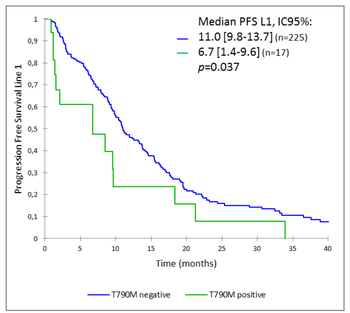


Figure 1: median overall survival (OS) and progression-free survival (PFS) according to T790M mutation status.

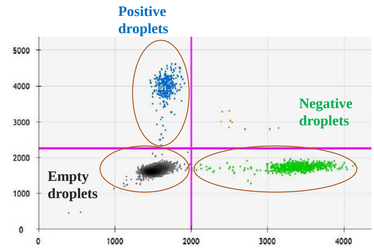


Figure 2: 2D representation of a T790M mutation positive case.

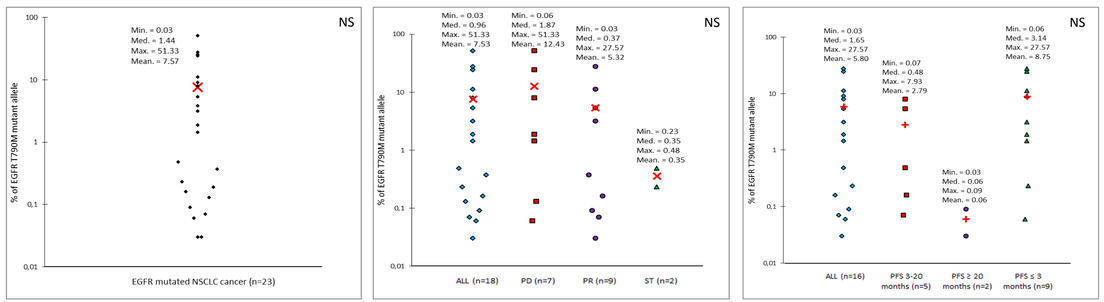


Figure 2: repartition of T790M mutation FA.
All patients (left); according to the type of response (middle) ; according to the time of response (right).
Mean FA is indicated by a red cross. PD= progressive disease, PR= partial response, SD= stable disease

In multivariate analysis, OS was associated with the presence of a pre-treatment T790M mutation with FA between 1-10% (HR 3; 95% CI 1.06-6.5, p = 0.04) or FA ≥ 10% (HR 16; 95% CI 5-47, p < 0.0001); PFS was associated with the presence of a pre-treatment T790M mutation only with FA ≥ 10% (HR 21; 95% CI 5-75, p < 0.0001).

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(1) Barlesi F, Lancet 2016; (2) Leduc C, Ann Oncol 2017