Circulating tumor DNA (ctDNA) in advanced non-small cell lung cancer (NSCLC) from HIV-infected patients is associated to shorter overall survival (OS): results from phase II trial (IFCT-1001 CHIVA)

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BACKGROUND

- In 2010, cancer represented 34% of the causes of death in France in HIV-infected population, and lung cancer was the first cause of mortality by cancer.
- The prognosis of non-small cell lung cancer (NSCLC) is worse in HIV-positive individuals. Some authors suggest that these poor outcomes may be related to interactions and additive toxicities of the cytotoxic and antiretroviral drugs. It is also likely that the disease is particularly aggressive. Recommendations for treatment of advanced NSCLC are lacking in this population, as HIV seropositivity is an exclusion criteria from most trials. There is a crucial need to identify new therapeutic targets in this specific population to improve their prognosis.
- We have previously showed in a retrospective cohort of 41 HIV-positive patients that mutation rates were 5.5% for *EGFR* and 11% for *KRAS* (Lavolé et al., Rev. Mal. Respir. 2014). However, few data are available on the molecular profile of NSCLC in HIV-positive population.
- Furthermore, circulating tumor DNA (ctDNA) is an approved biomarker to test the presence of *EGFR* mutations in advanced NSCLC, and it has been shown to be a prognostic marker in HIV-undetermined patients.
- Our goal was to assess its prognosis value and the molecular profile of NSCLC in HIV-positive patients.

METHODS

- 55 HIV-positive patients with advanced NSCLC were included in IFCT-1001 CHIVA phase II trial evaluating carboplatin AUC5 pemetrexed 500 mg/m2 every 3 weeks, followed by a maintenance with pemetrexed as first-line of treatment.
- Baseline blood samples were collected in all patients, and ctDNA was assessed by ultra-deep targeted NGS using a dedicated variant caller algorithm.
- For OS and PFS, univariate Cox models were applied to select the most promising prognostic variables (threshold p=0.20). A multivariate Cox model was then applied using a backwards procedure to adjust for potential confounders.

PATIENT CHARACTERISTICS

	All (N=55) N (%)
Sex	
Male	42 (76.4)
Female	13 (23.6)
Age	
Median	52.91
Range	38-67.5
Smoking history	
No	4 (7.3)
Yes	51 (92.7)
PS at inclusion	
0-1	46 (83.6)
2	9 (16.4)
Histology	
Adenocarcinoma	50 (90.9)
Sarcomatoid carcinoma	1 (1.8)
Others	4 (7.3)
Stage	
III	5 (9.1)
IV	50 (90.9)
Nadir CD4+ T-cell count	
Median	156
Range	0-822
CD4+ T-cell count	
Median	418
Range	18-1230
HIV viral load	
Median	39.5
Range	0-95499

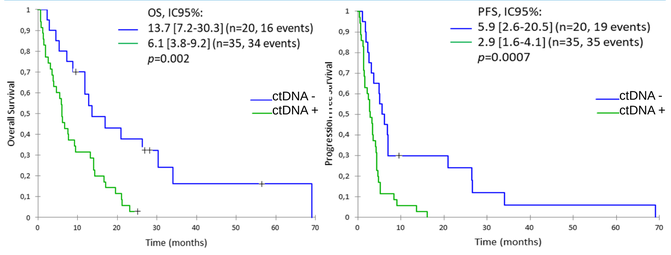
MOLECULAR CHARACTERISTICS

	N (%)
ctDNA detection	
+	35 (64)
-	20 (36)
Mutation detected	
TP53	27 (77)
KRAS	10 (28.6)
STK1	4 (11.4)
EGFR	2 (5.7)
NRAS	2 (5.7)
BRAF	2 (5.7)
MET	2 (5.7)
DDR2	1 (2.9)
HER2	1 (2.9)
FGFR1	1 (2.9)
FGFR3	1 (2.9)

ctDNA AND CLINIC PARAMETERS

	No ctDNA (N=20)	ctDNA detected (N=35)	p-value
Sex			
Male	17 (85)	25 (71.4)	0.33
Female	3 (15)	10 (28.6)	
Age			
Median	53.64	52.57	0.10
Range	46.1-67.5	38-66.5	
Smoking history			
Yes	18 (90.0)	33 (94.3)	0.62
No	2 (10.0)	2 (5.7)	
PS at inclusion			
0-1	17 (85)	29 (82.9)	0.41
2	3 (15.0)	6 (17.1)	
Histology			
Adenocarcinoma	19 (95)	31 (88.6)	0.79
Sarcomatoid	0	1 (2.9)	
Epidermoid	1 (5.0)	3 (8.6)	
Stage			
III	4 (20.0)	1 (2.9)	0.05
IV	16 (80.0)	34 (97.1)	
AIDS status			
CD4 count	383.5 [58-954]	456 [18-1230]	0.56
Nadir CD4	150.5 [0-631]	160 [0-822]	0.40

OS AND PFS



ANALYSIS OF OS

	Univariate Analysis			Multivariate Analysis (n=55)		
	HR	95% CI	p	HR	95% CI	p
Age						
≤ 50 yrs	1	-	-			
> 50 yrs	0.74	0.43-1.27	0.27			
Cancer history						
No	1	-	-	1	-	-
Yes	1.80	0.84-3.86	0.13	1.59	0.67-3.75	0.29
ECOG PS						
0/1	1	-	-	1	-	-
2	5.82	2.73-12.38	<.0001	4.10	1.62-10.36	0.003
CD4+						
≤200	1	-	-			
>200	0.87	0.45-1.69	0.68			
HIV Viral load						
≤50	1	-	-			
>50	0.95	0.47-1.91	0.89			
Highly active antiretroviral therapy						
No	1	-	-	1	-	-
Yes	0.20	0.04-0.87	0.03	0.61	0.06-5.72	0.66
AIDS						
No	1	-	-	1	-	-
Yes	1.59	0.89-2.84	0.12	1.75	0.89-3.42	0.10
ctDNA						
-	1	-	-	1	-	-
+	2.79	1.43-5.45	0.003	3.52	1.72-7.19	0.0006

ANALYSIS OF PFS

	Univariate Analysis			Multivariate Analysis (n=55)		
	HR	95% CI	p	HR	95% CI	p
Age						
≤ 50 yrs	1	-	-			
> 50 yrs	0.87	0.51-1.48	0.61			
Cancer history						
No	1	-	-	1	-	-
Yes	1.78	0.86-3.67	0.12	1.92	0.88-4.21	0.10
ECOG PS						
0/1	1	-	-	1	-	-
2	2.97	1.51-5.86	0.002	1.99	0.91-4.38	0.09
CD4+						
≤200	1	-	-			
>200	1.13	0.58-2.20	0.71			
HIV Viral load						
≤50	1	-	-			
>50	1.10	0.57-2.13	0.78			
Highly active antiretroviral therapy						
No	1	-	-			
Yes	0.50	0.12-2.10	0.34			
AIDS						
No	1	-	-	1	-	-
Yes	1.48	0.84-2.60	0.17	2.17	1.09-4.32	0.03
ctDNA						
-	1	-	-	1	-	-
+	2.87	1.52-5.44	0.001	4.31	2.06-8.99	<0.0001

CONCLUSIONS

ctDNA detection and quantification using ultra deep targeted NGS is an independent prognostic factor of OS and PFS in advanced NSCLC from HIV-infected patients.

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