MONITORING OF *ALK* FUSION AND MUTATIONS IN ADVANCED *ALK* POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

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BACKGROUND

- Liquid biopsies isolating exosomal RNA (exoRNA) and circulating free (cf) DNA from plasma can be used for detecting genomic alteration such as ***EML4-ALK* fusions** on RNA and ***ALK* resistance mutations** among *ALK* positive advanced NSCLC patients.
- The clinical utility of liquid biopsies for **response monitoring** is under investigation.

OBJECTIVE

- The aim of this study was to assess liquid biopsies as a **dynamic marker** of treatment efficacy in a prospective cohort of *ALK*-positive advanced NSCLC patients

PATIENTS AND METHODS

- Consecutive *ALK* positive NSCLC patients treated with ALK inhibitors (crizotinib, second and third generation ALK inhibitors) in Gustave Roussy were enrolled from August 2016.
- **Prospective blood samples** were collected after informed consent, for longitudinal analysis at diagnosis, at baseline of ALK inhibitors when available, during treatment and at progression.
- Exosomal RNA from plasma was used for detection of EML4-ALK fusion RNAs by the qPCR-based ExoDx Lung(ALK)™-test
- cfDNA and exoRNA was used to detect ALK-resistance mutations by ExoDx NGS sequencing.

ExoDx NGS sequencing panel	*ALK G1202R, L1196R, L1198F, E1197K, G1201E, L1196Q, A1200V, G1201E BRAF, KRAS, NRAS, EGFR and HER2 mutations*

Table 1: *Next generation sequencing (NGS)* ExoDx panel

RESULTS

- **32 patients** were included. The median follow-up (FU) was 14 months [95% CI 10-19].
- The median PFS was 39 months [95% CI 15-not reached (NR)]. The median OS was NR [95% CI NR-NR]. The mean duration of treatment was 12.7 months ± SD 9.3 months.
- **77 samples have been longitudinally collected**: 4 in treatment-naïve patients, 10 at baseline to treatment; 53 during treatment and 14 at progressive disease (PD). The median of samples per patient was 2 (range 1-5).

	ALK rearranged patients *N* = 32 (100%)
Sex	
Male	10 (31%)
Female	22 (69%)
Age at diagnosis	
Median (years, range)	52 (24-75)
Smoking status at diagnosis	
Non-smoker	17 (53%)
Smoker	15 (47%)
Histology	
Adenocarcinoma	32 (100%)
ALK detection	
ALK *IHC*	16 (62%)
ALK *FISH*	22 (69%)
Stage at diagnosis	
III	3 (10%)
IV	25 (86%)
Metastases sites**	
Median (Range)	1 (0-6)
Lung, pleural	8 (25%)
Bone	8 (25%)
Brain	7 (22%)
Nodal	5 (17%)
Previous lines	
Median	1 (0-8)
Current therapy	
Crizotinib	8 (25%)
2nd gen- ALK inhibitor	6 (19%)
3rd gen- ALK inhibitor	18 (56%)
Best response rate	
ORR	19 (59%)
Stable disease	7 (22%)
Progressive disease	3 (9%)

** *at baseline of ALK inhibitor*

Table 2: *Baseline characteristics*

ALK FUSION

ALK fusion RNA as dynamic marker of efficacy

- Nine out of 77 (12%) samples were positive for EML4-ALK:
  - N=5/10 collected at baseline to therapy
  - N=7/14 collected during therapy, at PD
- Six (67%) out of 9 positive on plasma were the EML4-ALK variant 3, and 3 (33%) the variant 1

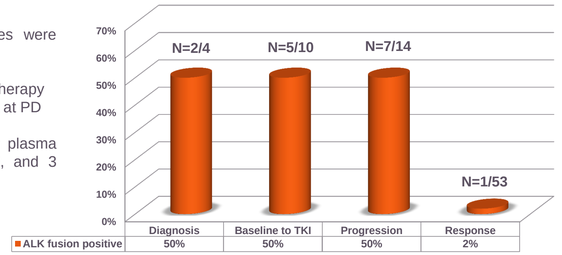

Figure 1: ALK fusion detection according to the collection time

- Fifty-two (98%) out of 53 samples collected **during objective response or stable disease** were negative
- **5/7 (71%)** ALK negative samples collected at PD:
  - n=3, isolated brain PD
  - n=1, oligo PD
  - n=1, slowly PD

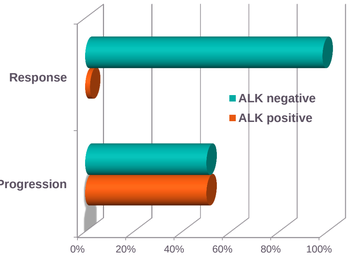

Figure 2: ALK fusion detection according to the radiological response at the collection time

ALK RESISTANCE MUTATION

Secondary mutations at progression

- The ALK resistance mutation panel was performed on 6 samples from patients with PD at time of collection (43%)

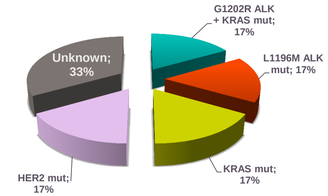

Figure 3: Secondary mutations detected at time of progressive disease

- **Two ALK resistance mutations** were detected (33,3%)

	ALK fusion	ALK mutation	Other mut. found
N# 1 PD to brigatinib	v.3	**G1202R**	KRAS mut (G13D)
N# 2 PD to crizotinib	v.1	**L1196M**	-

- **Other secondary mutations** were also found in 3 patients: 2 KRAS mutations (G13D and A11V) and 1 HER2 mutation (S310F)

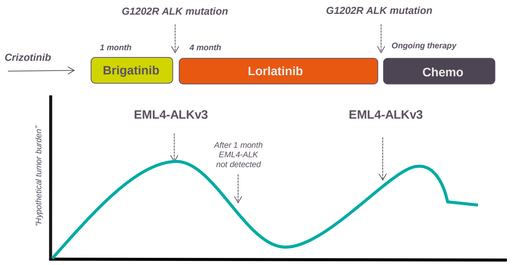

Figure 4: Schematic example of the longitudinal collection of plasma for ALK fusion and ALK resistance mutation in a patient of this cohort

CONCLUSION

✓ Monitoring of **ALK fusion on exosomal RNA** is feasible and closely correlated to disease control. **ALK resistance mutations can be detected on plasma.**
✓ This study is still ongoing for validating these findings in a larger population.

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