Racial differences in ALK gene alterations detected by tissue and liquid biopsy across patients with lung cancer.

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2024 World Conference on Lung Cancer
SEPTEMBER 7-10, 2024
SAN DIEGO, CA USA

INTRODUCTION

- ALK gene alterations occur in 2-4% of lung cancer patients and lead to constitutive activation of RAS-MAPK, PI3K-AKT and JAK-STAT pathways.
- Racial differences in ALK gene-altered lung cancers are not well defined.
- The objective of this study was to assess the frequency and type of ALK alterations observed in lung cancers across races.

METHODS

Patients with a primary lung cancer diagnosis (histology and stage agnostic) that underwent testing via Tempus xT/xR (tissue) or xF (liquid biopsy) assays (n=27,991) and had a confirmed pathogenic ALK gene alteration (SNVs, CNAs, or fusions) were retrospectively identified within the Tempus database (n=377). Pathogenic ALK gene alterations included single nucleotide variants (SNVs), copy number amplifications (>=8), and fusions. Patients were categorized by race (White, Black or African American [BAA], Asian Pacific Islander [API], unknown, or other) based on clinical records. Comparisons between races were performed using Chi-squared/Fisher's Exact tests with FDR correction.

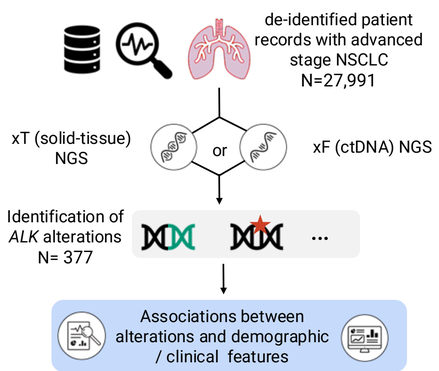

Figure 1. Study methodology.

SUMMARY

- In this large cohort of lung cancer patients, *ALK* fusions had the highest prevalence in Asian Pacific islanders (API) and the lowest prevalence in African American patients (BAA).
- The most common ALK gene alteration was EML4 fusions. BAA patients are more likely to have a unique set of fusion partners other than EML4-ALK.
- Some atypical fusion partners were observed in white and BAA patients that were not observed in other races, with further research needed to understand the clinical significance of these rearrangements.

RESULTS

	Overall N = 377[1]	White N = 177[1]	BAA N = 22[1]	API N = 26[1]	Other N = 21[1]	Unknown N = 131[1]	p-value[2]
Age at Diagnosis	59 (50, 69)	60 (51, 69)	55 (48, 66)	60 (53, 70)	51 (46, 63)	58 (50, 69)	0.3
Unknown	1	1	0	0	0	0	
Gender							0.3
Female	202 (54%)	94 (53%)	14 (64%)	16 (62%)	7 (33%)	71 (54%)	
Male	175 (46%)	83 (47%)	8 (36%)	10 (38%)	14 (67%)	60 (46%)	
Smoking Status							0.2
Never smoker	215 (65%)	97 (62%)	11 (50%)	16 (73%)	14 (74%)	77 (71%)	
Current/ former smoker	114 (35%)	60 (38%)	11 (50%)	6 (27%)	5 (26%)	32 (29%)	
Unknown	48	20	0	4	2	22	
TKI Exposure	6 (1.6%)	6 (3.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.2
Stage at biopsy							
Stage 4	197 (81%)	87 (80%)	11 (79%)	12 (80%)	14 (74%)	73 (84%)	
Stage 3	25 (10%)	9 (8.3%)	3 (21%)	1 (6.7%)	4 (21%)	8 (9.2%)	
Stage 1	13 (5.3%)	9 (8.3%)	0 (0%)	2 (13%)	0 (0%)	2 (2.3%)	
Stage 2	9 (3.7%)	4 (3.7%)	0 (0%)	0 (0%)	1 (5.3%)	4 (4.6%)	
Unknown	133	68	8	11	2	44	
Metastatic prior to biopsy	280 (74%)	130 (73%)	15 (68%)	18 (69%)	15 (71%)	102 (78%)	0.8
Histology							0.5
Adenocarcinoma	276 (82%)	126 (79%)	13 (72%)	19 (86%)	18 (90%)	100 (84%)	
Other	62 (18%)	33 (21%)	5 (28%)	3 (14%)	2 (10%)	19 (16%)	
Unknown	39	18	4	4	1	12	

[1] Median (IQR); n (%)
[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test

Table 1. Baseline clinical characteristics. 97% of patients with tissue testing had low TMB, 99% had stable MSI, and 70% had positive PDL-1.

- The frequency of ALK alterations varies significantly across race (P<0.001).
- The most common ALK alteration in API and other races was EML4 fusion (87%) versus 62% EML4 fusions in BAA.

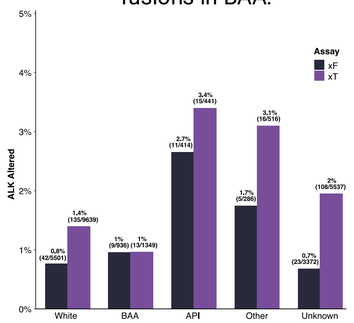

Figure 2. Prevalence of ALK alterations in ctDNA and tissue NGS. ALK alterations were noted in 1.3% of the cohort.

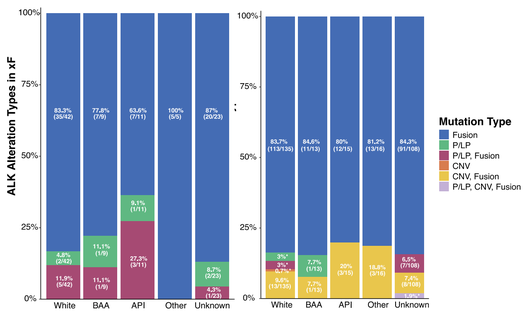

Figure 3. ALK alteration type according to race.

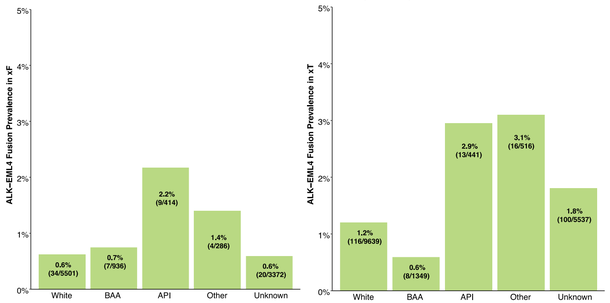

Figure 4. ALK fusion partners. API and others had the highest prevalence of ALK-EML4 fusions. Atypical gene fusion partners ACYP2, RMND5A, BABAM2, MYT1L and TPR were observed only in BAA patients. RNA fusions partners of SOS1, KLC1, NPM1, PRKAR1A were observed only in white patients.

	Overall N = 62	White N = 42	BAA N = 9	API N = 11	p-value[1]	q-value[2]
PIK3CA	5 (8.1%)	2 (4.8%)	1 (11%)	2 (18%)	0.2	0.5
BRCA2	1 (1.6%)	0 (0%)	1 (11%)	0 (0%)	0.15	0.5
FLT3	1 (1.6%)	0 (0%)	1 (11%)	0 (0%)	0.15	0.5
MSH2	1 (1.6%)	0 (0%)	1 (11%)	0 (0%)	0.15	0.5
NF1	1 (1.6%)	0 (0%)	1 (11%)	0 (0%)	0.15	0.5
	Overall N = 163	**White** N = 135	**BAA** N = 13	**API** N = 15	**p-value[1]**	**q-value[2]**
BCORL1	3 (1.8%)	1 (0.7%)	2 (15%)	0 (0%)	0.019	0.5
ESR1	3 (1.8%)	1 (0.7%)	2 (15%)	0 (0%)	0.019	0.5
POLE	6 (3.7%)	4 (3.0%)	2 (15%)	0 (0%)	0.11	0.5
RBM10	7 (4.3%)	5 (3.7%)	2 (15%)	0 (0%)	0.15	0.5
SYNE1	3 (1.8%)	1 (0.7%)	2 (15%)	0 (0%)	0.019	0.5
MSH2	2 (1.2%)	0 (0%)	0 (0%)	2 (13%)	0.014	0.5
TNFAIP3	3 (1.8%)	1 (0.7%)	1 (7.7%)	1 (6.7%)	0.077	0.5

Table 2. Co-mutations in ALK alterations. Somatic alterations (short variants and CNVs) in 5% or more of patients of known races in xF (top) and xT (bottom).
[1.] Fisher's exact test, [2.] FDR correction for multiple testing

ACKNOWLEDGMENTS

We thank Adam J. Hockenberry from the Tempus Science Communications team for poster development.

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