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Next-generation sequencing analysis of gene fusions in non-small cell lung cancer

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Abstract: *In non-small cell lung cancer (NSCLC) gene fusions involving ALK, ROS1, RET, NTRK and MET represent clinically relevant molecular alterations. Their identification is essential for molecular characterization and guide treatment selection, particularly through the use of targeted therapies. The aim of this study was to evaluate the presence of gene fusion in patients with NSCLC using next-generation sequencing (NGS). The DNA and ARN samples from 1200 patients with stage III and IV cancer were subjected to detection of 137 fusion genes and point mutation in 42 genes using “SOPHiA DDM™ Solid Tumor Solution Kit” and NextSeq 2000 platform. Among the identified fusions, MET exon 14 skipping was the most prevalent single event, occurring in 12 cases (22.22%). Within the ALK fusion cluster totaling 15 cases (27.77%), the EML4-ALK variant was highly predominant, accounting for 12 cases while DCTN1, RANBP2, and an unconventional ALK-PJA2 fusion were each detected in single case. The ROS1 fusion group exhibited the highest diversity in partner genes, totaling 9 cases (16.66%). NTRK family displayed distinct fusion types identified in 5 cases (9.25%), while in RET family driven by KIF5B-RET and CCDC6-RET fusions were observed in 4 cases (7.42%). EGFR alterations included both EGFRvIII (3 cases, 5.55%) and a rare EGFR - AKT2 fusion (1 case). Finally, low-frequency fusions were noted in BICC1 (3 cases, 5.55%), alongside single occurrences of FGFR3 and BRAF. The genomic analysis of the cohort revealed a various landscape of oncogenic gene fusions and skipping events across several key driver genes that have distinct therapeutic implications.*

• Introduction

Lung cancer is the leading cause of cancer death in the world ranking 4th in terms of cancer incidence among men and 1st among women in Romanian population. The aim of this study was to evaluate the presence of gene fusion in patients with NSCLC using NGS technology.

• Material and method

The DNA and ARN samples from 1200 patients with stage III and IV cancer (Table 1.) were subjected to detection of 137 fusion genes and point mutation in 42 genes using “SOPHiA DDM™ Solid Tumor Solution Kit” and NextSeq 2000 platform.

Table 1. Demographic and clinical characteristics of the study population (n = 1200)

Variable	Values				
	Mean	Median	SD	Min	Max
Age (years)					
Male	65,96	67	9,16	30	92
Female	65,96	67	9,17	36	88
Gender					
Male	797 (66,41%)				
Female	403 (33,59%)				
Smoking habits					
Smokers: male/female	62/23				
Non-smokers: male/female	122/43				
Staging					
III	47 (3,91%)				
IV	1153 (96,09%)				
EGFR status					
Pozitive	174 (14,5%)				
Negative	1026 (85,5%)				
NSCLC type					
LUAD	950 (79,16%)				
LUSQ	250 (20,84%)				

• Results and discussions

Out of the total population analysed the vast majority of patients accounting of 85.5% were EGFR negative, in contrast only 14.5% of the patients tested positive for EGFR mutations.(Fig.1)

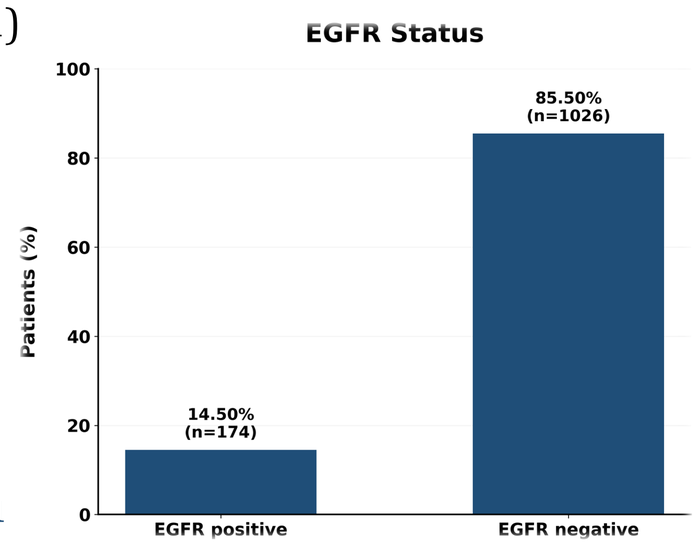


Fig.1

MET exon 14 skipping and ALK fusions are the most prevalent among the identified genetic alterations followed by varying frequencies of ROS1, NTRK, RET, EGFR and other low frequency occurrences like BICC1, FGFR3, and BRAF. (Fig.2)

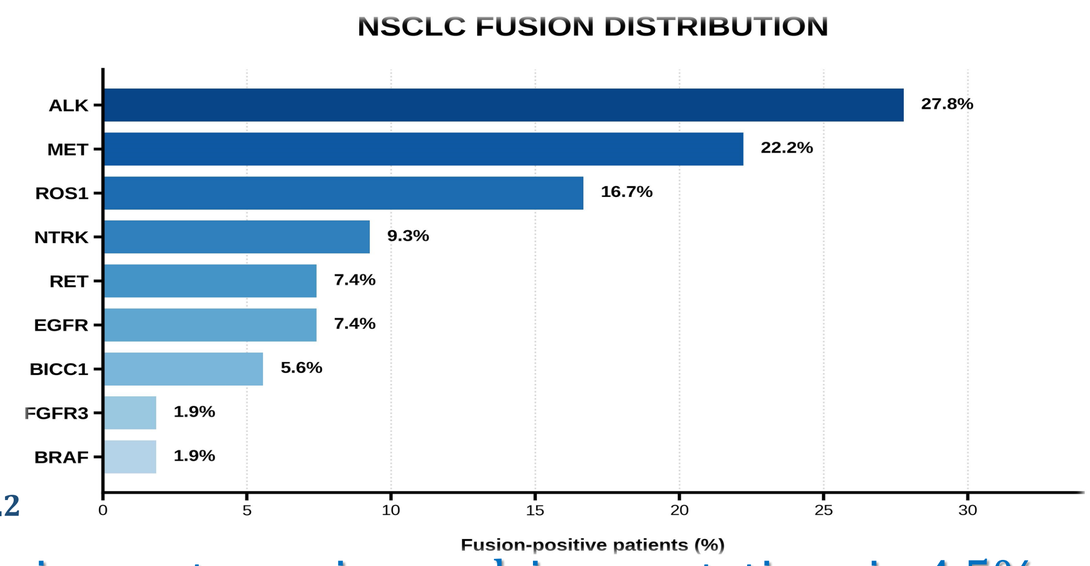


Fig.2

Conclusion. Our results showed that oncogenic gene fusions act as primary driver mutations in 4.5% of NSCLC cases guiding the use of specialized tyrosine kinase inhibitors.