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Frequency of Driver Mutations Across Disease Stages in Slovenian Non-Small Cell Lung Cancer Patients

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1 BACKGROUND

In Slovenia, reflex and routine NGS testing was introduced in 2022 for all newly diagnosed non-squamous NSCLC, regardless of the disease stage. More than 90% of all samples are analyzed in a single national laboratory (approximately 800–900 samples annually).

Around 40% of all Slovenian lung cancer cases are diagnosed at University Clinic Golnik (UCG), a single high-volume center.

This study trial provides the first comprehensive analysis of genetic biomarkers in Slovenian non-squamous NSCLC patients (Slovenian cohort). For patients diagnosed at UCG (UCG cohort), molecular alteration frequencies and their distribution across disease stages are analysed.

2 METHODS

Initial diagnostic biopsies from patients with non-squamous NSCLC were collected between January 2022 and December 2024. In total, 2,559 patients underwent NGS testing. Of these, 898 (35%) were diagnosed at UCG, enabling more detailed clinical data collection. Demographic characteristics and stage distribution are presented in *Table 1*.

NGS was performed using the Thermo Fisher Oncomine Precision Assay on the Genexus® system. This study reports the frequency and distribution of actionable oncogenic drivers in the Slovenian cohort and assesses driver prevalence by disease stage—early (I–IIIA) versus late (IIIB–IV)—within the UCG subgroup. All lung cancer stages were assigned according to the 8th edition of the TNM staging groups.

3 RESULTS

Targetable driver alterations were identified in 1,504 (59%) samples in the Slovenian cohort. Overall frequencies are summarized in *Table 2*. A detailed analysis across disease stages was performed for the UCG cohort. Nearly half of UCG patients (49.7%, n=446) presented with early-stage disease, most commonly Stage I (n=307, 34.2%), reflecting the center's expertise in detecting small lesions. The distribution of targetable driver alterations across disease stages is shown in *Table 3*. Broadly, alteration frequencies were either comparable or slightly higher in late-stage patients. For several rare alterations, however, the observed frequencies were too low to allow reliable conclusions.

Demographic and clinical characteristics	Slovenian cohort	UCG cohort
Number of patients, n	**2559**	**898**
Mean age, years (range)	**70 (31-96)**	**68.3 (42-92)**
Sex, male (%)	**52%**	**52.1%**
Smoking status		
Smoker/ex-smoker, n (%)	No data	717 (80%)
Non-smoker, n (%)		161 (18%)
Passive smoker, n (%)		18 (2%)
Histology of non-squamous NSCLC		
Adenocarcinoma, n (%)	No data	839 (93%
Not other specified (NOS), n (%)		59 (7%)
Frequency of targetable driver alterations,%	59%	63%
Disease stage distribution, N (%)		
Early		**446 (49.7%)**
Stage I		307 (34.2%)
Stage II		76 (8.5%)
Stage IIIA	No data	63 (7.0%)
Late		**448 (49.9%)**
Stage IIIB, IIIC		46 (5.1%)
Stage IV		402 (44.8%)
No data		**4 (0.4%)**

◀ *Table 1:*
Demographic and clinical data for the studied cohorts. Of the total Slovenian cohort of NSCLC patients that underwent molecular diagnostics between 2022 and 2024, a subset of patients (N=898) was diagnosed and treated at the University Clinic Golnik.

Gene	N (%)
KRAS mutation	922 (36.03 %)
EGFR mutation	356 (13.91 %)
ALK fusion	74 (2.89 %)
BRAF V600E	42 (1.64 %)
MET Ex14 Skipping mutation	42 (1.64 %)
RET fusion	32 (1.25 %)
ROS1 fusion	17 (0.66 %)
ERBB2 mutation	16 (0.63 %)
NRG1 fusion	8 (0.31 %)
NTRK 1/2/3 fusion	1 (0.04 %)

◀ *Table 2:*
Frequency of targetable driver alterations in 2,559 Slovenian non-squamous NSCLC patients.

	UCG cohort (all stages)	Early stage	Late stage
KRAS mutation, %	37.3	39.0	35.3
EGFR mutation, %	14.8	13.9	15.3
ALK fusion, %	3.5	3.1	3.7
BRAF V600 E mutation, %	1.8	1.3	2.2
MET Ex14 Skipping mutation, %	2.4	3.5	1.3
RET fusion, %	1.2	1.5	0.9
ROS1 fusion, %	0.7	0.4	0.9
ERBB 2 mutation, %	0.7	0.4	0.9
NTRK 1/2/3 fusion, %	0.1	0.2	0.0

◀ *Table 3:*
Frequency of targetable driver alterations across disease stages in 898 patients, diagnosed at University Clinic Golnik.

CONCLUSIONS

This study provides invaluable insight into biomarker frequencies within one of the largest and most homogeneous national NSCLC cohorts assessed using a single NGS assay. Notably, the cohort includes a substantial proportion of early-stage patients, a group that is rarely tested in routine practice worldwide. We observed broadly comparable frequencies of driver mutations across disease stages, indicating that oncogenic alterations may be present early in cancer development. These findings support the future evaluation of biomarker-guided targeted therapies in early-stage NSCLC.

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