Molecular biomarker testing in Slovenian non-small cell lung cancer patients in early and late stages of the disease

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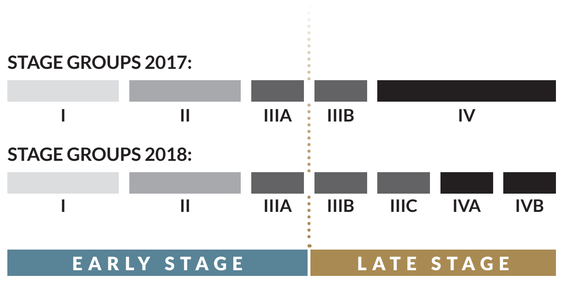
INTRODUCTION

Molecular biomarkers in non-small cell lung cancer (NSCLC), primarily involving pathogenic alterations in key oncogenes, play a critical role in personalizing cancer treatments. Initially important only for advanced stages, they are now essential in early-stage treatment decisions. In Slovenia, testing for common molecular alterations and PD-L1 expression has been gradually implemented into a routine practice since 2010 for all newly diagnosed non-squamous NSCLC patients, regardless of disease stage. This study aims to report the testing rates and observed frequencies of these molecular alterations.



Note: In 2018, staging categories changed.
Patients in 2017 were classified only as stage IIIA, IIB and IV, while from 2018 onwards, stages IIiC, IVA and IVB were assigned.

METHODS

Biomarker and clinical data for about 1600 patients ***(Table 1, Figure 1)*** was collected from the clinical registry of University Clinic Golnik, the largest lung cancer center in Slovenia. Samples are from biopsies of newly diagnosed NSCLC patients with adenocarcinomas and not-otherwise-specified (NOS) histologies admitted between January 2017 - December 2021. Each sample was tested for:

1. Variants:

- epidermal growth factor receptor (EGFR)
- Kirsten rat sarcoma viral oncogene (KRAS)
- v-raf murine sarcoma viral oncogene homolog B1 (BRAF)

2. Fusions:

- anaplastic lymphoma kinase (ALK)
- c-ros oncogene 1 (ROS1)

3. PD-L1 gene expression

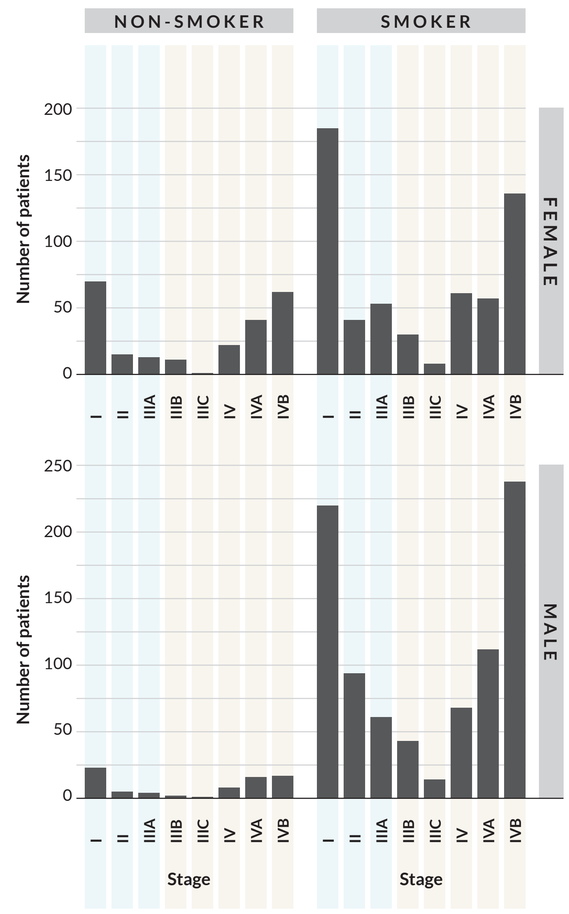
Testing was performed stepwise, the methods were PCR (for EGFR, KRAS and BRAF) and IHC (for ALK, PD-L1, and ROS1). Driver mutations were assumed to be mutually exclusive. PD-L1 data is grouped according to NCCN guidelines[1]: "zero" (0 %), "low" (≥1-49 %) and "high" (≥50 %).

Most tumor stages (1599/1615, 99%) were assigned according to the 8th edition of TNM staging groups[2], except patients admitted in 2017 who were classified according to the 7th edition. Patients with unknown staging were excluded. Stage groups were further classified as either early stage (I-IIIA) or late stage (IIIB- IVB) of the disease, which are designations used for the entirety of this study.

Kaplan-Meier curves for early and late stage patients were calculated for the three biomarkers with sufficient data (EGFR, KRAS, ALK). The frequency of patients who experienced a metastatic event and received targeted or non-targeted therapy in each treatment line was calculated and visualized. The data was processed in R, coupled with additional packages ggsurvfit, ggplot2, tidyr and survival.

		Female	Male
Age (years)	Min.	32	36
	Mean	66.78	67.43
	Max.	89	93
Stage	Early stage	345	354
	Late stage	416	484
Smoking status	Non-smoker	224	68
	Smoker	532	768
	Unknown	5	3
Biomarkers positive/total (perc. %)	EGFR	144/745 (19.30 %)	57/826 (6.90 %)
	KRAS	294/740 (39.70 %)	339/820 (41.30 %)
	ALK	31/729 (4.30 %)	17/808 (2.10 %)
	ROS1	17/728 (2.30 %)	6/805 (0.70 %)
	PDL1	331/543 (61.00 %)	406/689 (58.90 %)
	BRAF	9/622 (1.40 %)	7/638 (1.10 %)

▲ ***Table 1.***
Demographic overview of the dataset.



▲ ***Figure 1.***
Distribution of patients by stage, smoking status, and gender.

RESULTS

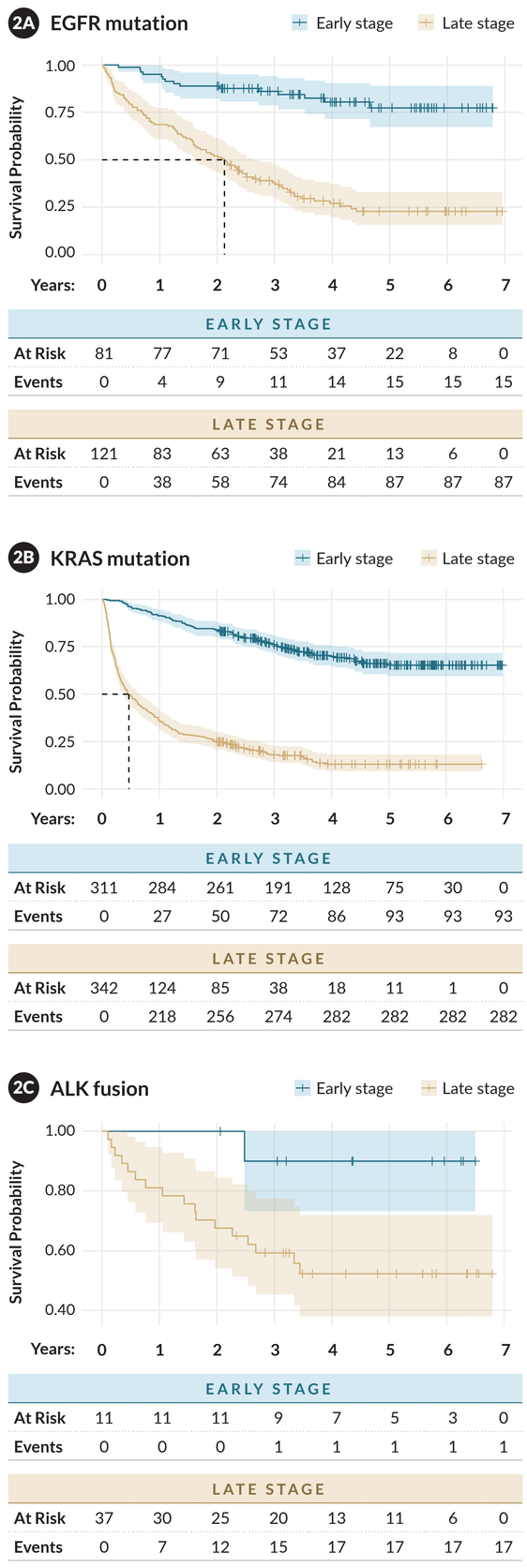
A total of 1,615 patients were tested for at least one biomarker, representing 91% of all patients with matching disease indications diagnosed at the center over a five-year period. Notably, 43% of these patients were in the early stages of the disease (n=699), with the majority in Stage I (n=440, 27%). This reflects the center's expertise in diagnosing small lesions. Frequencies of detected biomarkers and PD-L1 expression measurements are given in ***Table 2***. In all subgroups but KRAS and ROS1, late stage patients had higher rates of molecular alterations and were more likely PD-L1 high.

Kaplan-Meier survival plots ***(Figure 2)*** indicate that the median survival for early-stage patients with any of the measured biomarkers exceeds seven years. In contrast, survival outcomes for late-stage patients vary significantly, with KRAS-positive patients having the shortest median survival of 6 months. Notably, the median survival for late stage ALK-positive patients cannot be determined, as over half of these patients survive beyond the seven-year follow-up period of the study, which may be attributed to the sequential use of multiple available ALK inhibitors.

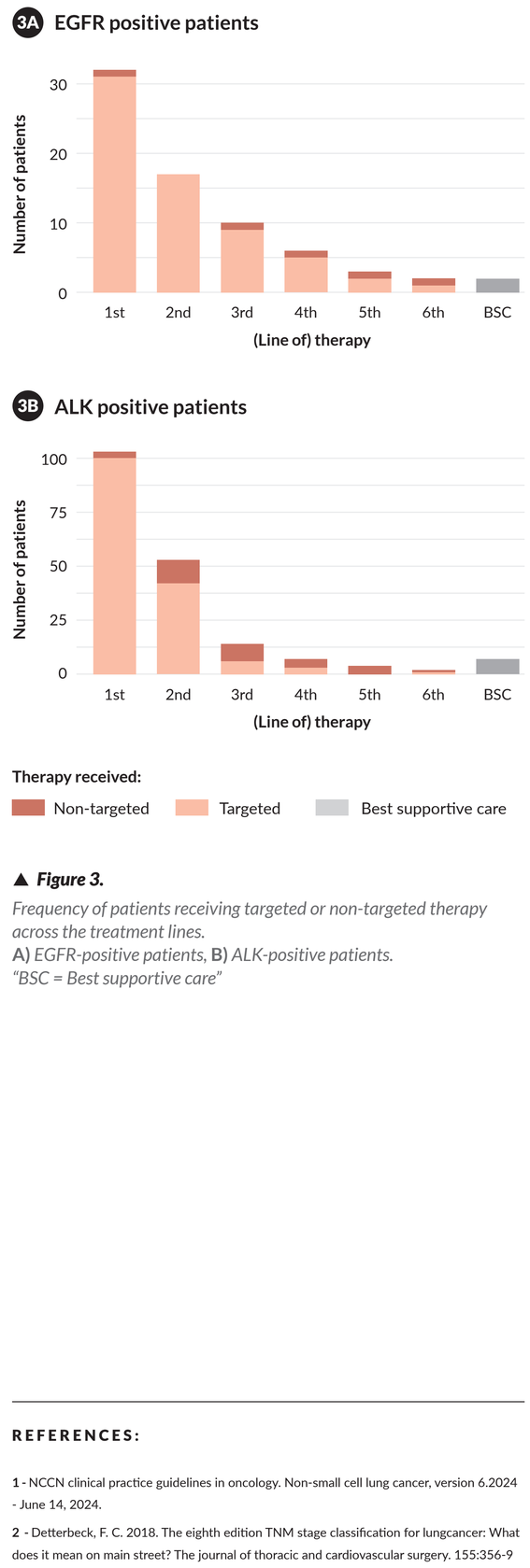
To evaluate the impact of biomarker measurements on treatment decisions, we analyzed the therapies received by late-stage patients who tested positive for a biomarker. Over 95% of patients testing positive for a molecular biomarker received a corresponding targeted therapy in the early lines of treatment ***(Figure 3)***. Although ***Figure 3*** focuses on EGFR- and ALK-positive patients, a similar trend was observed for those with ROS and BRAF alterations. It is important to note that no KRAS inhibitors were approved during the period covered by this study, which may contribute to the poor relative survival of this group relative to the other biomarker groups.

▼ ***Table 2.***
Percentage of patients (N=1599) testing positive for each biomarker, categorized by disease stage. The mean percentage represents the overall frequency.

	Mean	Early stage	Late stage
EGFR	12.7 %	11.6 %	13.8 %
KRAS	40.4 %	42.4 %	39.1 %
ALK	3.2 %	1.6 %	4.3 %
ROS1	1.5 %	2.0 %	1.0 %
BRAF	1.3 %	0.9 %	1.5 %
PD-L1 negative (0 %)		49.2 %	33.3 %
PD-L1 low (1-49 %)		27.1 %	26.6 %
PD-L1 high (≥ 50 %)		23.6 %	40.1 %



▶ ***Figure 2.***
Kaplan-Meier overall survival curves for early- and late-stage patients that tested positive for **A)** *EGFR mutation,* **B)** *KRAS mutation, or* **C)** *ALK fusion. The dashed line indicates median survival.*



▲ ***Figure 3.***
Frequency of patients receiving targeted or non-targeted therapy across the treatment lines.
A) *EGFR-positive patients,* **B)** *ALK-positive patients.*
"BSC = Best supportive care"

CONCLUSIONS

The 1600 patients described in this study represent around 40% of all NSCLC cases diagnosed in Slovenia in the 5 year period. The University Clinic Golnik specializes in diagnosing small or early-stage tumors, leading to a high frequency of early-stage disease in the dataset.

These findings offer insights into molecular biomarker rates from a large, homogeneous population, notably including early-stage cases, which are of particular significance since they are rarely reported globally.

More than 95% of late-stage patients with identified targetable biomarkers received targeted therapy in the early lines of treatment.

Kaplan-Meier analysis of overall survival (OS) for late-stage NSCLC patients shows the longest median survival for ALK-positive patients (~3.5 years), compared to EGFR (~2 years) and KRAS (~0.5 years).

Biomarker testing in both early and late stage NSCLC is crucial to providing patients with the best therapies, particularly in this disease setting where many treatment options exist and many more (i.e pan/multi-KRAS inhibitors) are in active clinical development.

REFERENCES:

1 - NCCN clinical practice guidelines in oncology. Non-small cell lung cancer, version 6.2024 - June 14, 2024.

2 - Detterbeck, F. C. 2018. The eighth edition TNM stage classification for lungcancer: What does it mean on main street? The journal of thoracic and cardiovascular surgery. 155:356-9