Neoplasma 2024; 71(5): 498–508

doi:10.4149/neo_2024_240625N272

The real-world comparison of non-small cell lung cancer survival outcomes depending on immunotherapy treatment and PD-L1 expression level

Martina ONDRUŠOVÁ[1,2], Martin SUCHANSKÝ[1], Soňa VÁNDOR SVIDOVÁ[1], Gabriela CHOWANIECOVÁ[3], Bela MRIŇÁKOVÁ[4], Monika SEKEREŠOVÁ[5], Dominik JUSKANIČ[6,7], Dalibor ONDRUŠ[4,#,*], Michal ŠENITKO[8,9,#,*]

[1]Pharm-In, Ltd., Bratislava, Slovakia; [2]Faculty of Public Health, Slovak Medical University, Bratislava, Slovakia; [3]Specialized Hospital of St. Zoerardus, Nitra, Slovakia; [4]1st Department of Oncology, Comenius University, Faculty of Medicine and St. Elisabeth Cancer Institute, Bratislava, Slovakia; [5]Department of Pathology, Faculty Hospital Nitra, Nitra, Slovakia; [6]JESSENIUS-Diagnostic Center, Nitra, Slovakia; [7]Faculty of Medicine, Slovak Medical University, Bratislava, Slovakia; [8]Division of Pulmonary and Critical Care Medicine, University of Mississippi Medical Center, Jackson, Mississippi, United States; [9]Hospital Bory, Bratislava, Slovakia

**Correspondence: dalibor.ondrus@fmed.uniba.sk; senitko@gmail.com*
[#]Contributed equally to this work.

Received June 25, 2024 / Accepted October 25, 2024

The incidence and mortality trends of lung cancer in Slovakia are not favorable. In our single-center, non-interventional retrospective cohort study, we provide comprehensive information about Slovakia's non-small cell lung cancer (NSCLC) patient population. We evaluated how the introduction of immunotherapy agents affected the survival of NSCLC patients and tried to identify whether the PD-L1 expression level was associated with a negative patient survival effect. The demographics, results of histological and immunohistochemical (PD-L1) examinations, and information about treatment (immunotherapy or standard of care (SOC)) were recorded. In males, squamous cell carcinomas occurred more often than adenocarcinomas (54.40% and 45.08%, respectively), in females, adenocarcinomas clearly dominated (71.88% vs. 27.08%, respectively). The overall proportion of adenocarcinomas was 53.98%. NSCLC patients with stage III and IV treated with SOC treatment (n=54) showed significantly worse overall survival than patients with immunotherapy (n=9) (p=0.026). The comparison of immunotherapy-treated (n=7) and SOC-treated (n=32) adenocarcinoma patients stage III and IV showed similar results (p=0.046). The negative effect of PD-L1 expression level on survival of females with NSCLC and females with adenocarcinoma was visible already at the TPS level of 20-25%. In males with NSCLC, the negative effect was visible at a TPS level of 70–90%. Our results confirm the positive impact of immunotherapy in real-world conditions and show different effects of PD-L1 expression level on patients' survival depending on sex and histology. Determination of different PD-L1 expression breaking points in males and females with NSCLC is a solid starting point for more research on this topic.

Key words: non-small cell lung carcinoma; adenocarcinoma; squamous cell carcinoma; immunotherapy; programmed cell death 1 ligand; survival

Lung cancer (LC) is the 3rd most common malignancy worldwide in both males and females. According to the International Agency for Research on Cancer WHO, estimates for 2022 LC represented 12.4% of all new cancer cases in the world and accounted for 18.7% of all cancer deaths [1].

Primary lung malignancies are classified as non-small cell lung carcinoma (NSCLC), small cell lung carcinoma, and other carcinomas. NSCLCs account for 80–85% of LCs and are further histologically categorized into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and other relatively rare subtypes [2–6]. Adenocarcinomas and squamous cell carcinomas are the most common subtypes of NSCLC [7]. According to the EUROCARE-5 study, adenocarcinomas were more frequent among females and squamous cell carcinomas among males [8]. In the Slovak Republic, squamous cell carcinomas were the most common subtype in males in 1978–1995 (57.1%). In females, the frequency of adenocarcinomas and squamous cell carcinomas was almost the same (32.2% and 31.9%, respectively) [9].

Several immune checkpoints play a role in standard therapeutic algorithms in the treatment of NSCLC. An important inhibitor checkpoint is the programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) pathway [10, 11].

PD-1 is a negative regulator of T-cell activity that limits the activity of T cells via interaction with its two ligands:

PD-L1 and PD-L2 [12, 13]. After interaction with a ligand, PD-1 inhibits kinase signaling pathways that normally lead to T-cell activation. This mechanism is important in the tumor microenvironment where tumors can adopt certain immune checkpoint pathways as a major mechanism of immune resistance. PD-L1 expressed by tumors interacts with PD-1 on T cells to suppress T-cell effector function [13]. Anti-PD-1/PD-L1-based agents that block signaling at this immune checkpoint have shown promising activity and are currently FDA- and EMA-approved treatment options for a broad range of cancer types [11, 14].

The expression of PD-1 ligands differs in various types of human tumors. Understanding the expression patterns may be essential for determining the relevance of therapeutic blockade of this pathway [15]. In NSCLC patients, positive PD-L1 expression is associated with more aggressive pathological features and poorer prognosis in advanced stages [16].

Immune checkpoint inhibitors (ICIs) of the PD-1 axis represent an important improvement in the management of NSCLC. In patients, whose tumors express PD-L1 on at least 50% of cells, ICIs have been shown to improve overall survival compared to chemotherapy in first-line therapy [10].

In the Slovak Republic, the incidence and mortality trends of LC are not favorable [17]. The last statistically processed and published national hard data for the LC incidence are from 2014. In that time there were n=2,461 newly diagnosed cases (1,789 cases in males and 672 in females), which represents a standardized incidence (ASR-W) of 43.58/100,000 in males and 12.53/100,000 in females [17]. LC incidence estimates for 2024 published by the Slovak National Oncology Register (NOR) predict n=3,233 cases in females and males combined (n=2,239 cases in males, ASR-W 41.64/100,000 and n=994 cases in females, ASR-W 14.45/100,000) [18].

Data on LC mortality is published annually by the Statistical Office of the Slovak Republic. The mortality in men for 2023 was n=1,385 cases and the mortality in women for 2023 was n=719 cases [19].

The possibilities of immunotherapy at the time of the data collection were limited [20]. Data for our study were collected during 2020 and 2021. During this period, pembrolizumab as the first-line of treatment, was available only for patients with a tumor proportion score (TPS) ≥ 50% pending approval of a particular health insurance company. Currently, the ICI pembrolizumab, the drug most frequently used in our study, is indicated as the first-line monotherapy treatment for patients, whose tumors express PD-L1 on at least 50% of cells, or in combination with chemotherapy for patients with advanced stage of NSCLC without EGFR, ALK, or ROS1 mutations [20].

Even though there is enough data on immunotherapy from numerous clinical trials, real-world comparisons of treated and untreated patients are lacking. In our non-interventional retrospective cohort study, we intended to evaluate how the introduction of immunotherapy agents affected the survival of NSCLC patients.

Patients and methods

Study design. This is a non-interventional retrospective cohort study comparing the survival of patients with newly diagnosed NSCLC (ICD-10 code C34) based on the results of histological and selected immunohistochemical examinations. The collected data on histopathology and PD-L1 expression came from the Department of Pathology, Faculty Hospital Nitra, Slovakia, data on TNM staging from JESSENIUS-Diagnostic Center, Nitra, Slovakia, and information about treatment was obtained from the Specialized Hospital of St. Zoerardus, Zobor, Nitra, Slovakia. All three centers include the geographical area of one district in Slovakia (Nitra, n=164,734 residents in 2023) [21]. The study complied with all applicable legal privacy requirements omitting any potential subject identification. Participating center granted permission from the local institutional review board to use medical chart data.

Ethical consideration. The study was approved by the Ethics Committee of Faculty Hospital Nitra, Slovakia, on February 28, 2024, and follows the Declaration of Helsinki ethical guidelines.

Participants and setting. Histological data of all patients newly diagnosed with LC (ICD-10 code C34) between January 1, 2020, and December 31, 2021, were collected. The end of the follow-up period was September 1, 2023. The study population consisted of a general (non-selective) sample, i.e. all patients with newly diagnosed LC in a single center of Faculty Hospital Nitra, Slovakia, who met the eligibility criteria.

Inclusion and exclusion criteria. The inclusion criteria were as follows: every new unique primary histologically confirmed LC diagnosed within the defined time frame, with TNM staging based on CT examination.

The exclusion criteria were: only cytologically verified cases (the IHC analysis used in this study is validated only for histological samples); neuroendocrine carcinomas or benign tumors; metastases of other malignancies to the lungs; patients with known cases of malignancy that underwent repeat histological evaluation. From the survival analysis we have also excluded patients with the inability to perform PD-L1 testing from the tissue obtained from the metastatic sites of lung carcinomas to other organs; and patients with the inability to determine TNM staging based on CT imaging (i.e., CT scan was not performed within a defined interval of 1 month around the performed histological examination of a newly diagnosed patient).

Primary and secondary objectives. The primary objective of the study was to compare the survival of patients with different histological types of NSCLC in regard to the treatment with an ICI or standard of care (SOC). The secondary objective was to identify whether the PD-L1 expression level is associated with a negative patient survival effect. Additional objectives were to describe the epidemiological trend of the whole Slovak population of LC patients and to characterize

the regional profiles of all patients in the study: histological type of LC, PD-L1 TPS, and clinical stage at diagnosis. The TPS <1% was considered negative and 1–100% was considered positive.

Variables and measurement. At the defined times and periods, the following variables were captured: The subjects' demographics recorded at diagnosis included sex, age, date of diagnosis, date of death (in case of patients' death during the defined period), detailed ICD-10 code and a complex result of microscopic examination, including histological description and PD-L1 expression level. The LC diagnosis was determined based on a detailed description of the histological and immunohistochemical (PD-L1) examination of the primary LC by a pathologist. The PD-L1 expression level was measured by immunohistochemical method (IHC). IHC analysis was conducted using IVD Dako PD-L1 22C3 (mouse monoclonal primary anti-PD-L1 antibody) assay on the Dako Autostainer Link 48 (Dako; Agilent Technologies, Inc.) with the EnVision FLEX visualization system. The detection and quantification of immunoreactivity were done according to the manufacturer's instructions. Tissue sections (4 μm thick) were made from the formalin-fixed, paraffin-embedded tissue specimen blocks. Human tonsil tissue was used as an external control. A minimum of 100 viable tumor cells were assessed. PD-L1 expression in tumor cells was evaluated according to the current guidelines [22], and the report included the proportion of tumor cells with partial or complete membrane staining-TPS. This staining was then classified into three groups according to the TPS: negative (0 and <1%); low expression (1–49%); and high expression (≥50%). For patients with PD-L1 expression above 50%, the information about immunotherapy was recorded. The date of diagnosis was defined as the date of release of the examination result by the pathologist. In order to determine the clinical stage of the disease, information about the TNM stage was added by a radiologist and based on the description of the computed tomography (CT) image of the lungs. The CT examinations were performed at the time of histological diagnosis or at most one month before/after the date of histological diagnosis. A clinical oncologist validated the patients' TNM stage and added information about the treatment and the date of death.

Immunotherapy and SOC treatment. The immune checkpoint inhibitor used in our study was pembrolizumab monotherapy, with the majority in first-line and minority in second-line metastatic NSCLC, exclusively in patients with PD-L1 TPS ≥50%. Not all patients with PD-L1 ≥50% received pembrolizumab, both because of clinical criteria (poor performance status, symptomatic brain metastases, autoimmune disease, or corticosteroid treatment) and because of unclear rules for approval of immunotherapy by health insurance. Combination chemotherapy and immunotherapy were not used in this cohort. Standard chemotherapy and radiotherapy were used, and standard targeted drugs were available without restriction in patients with genetic alterations of EGFR, ALK, or ROS1.

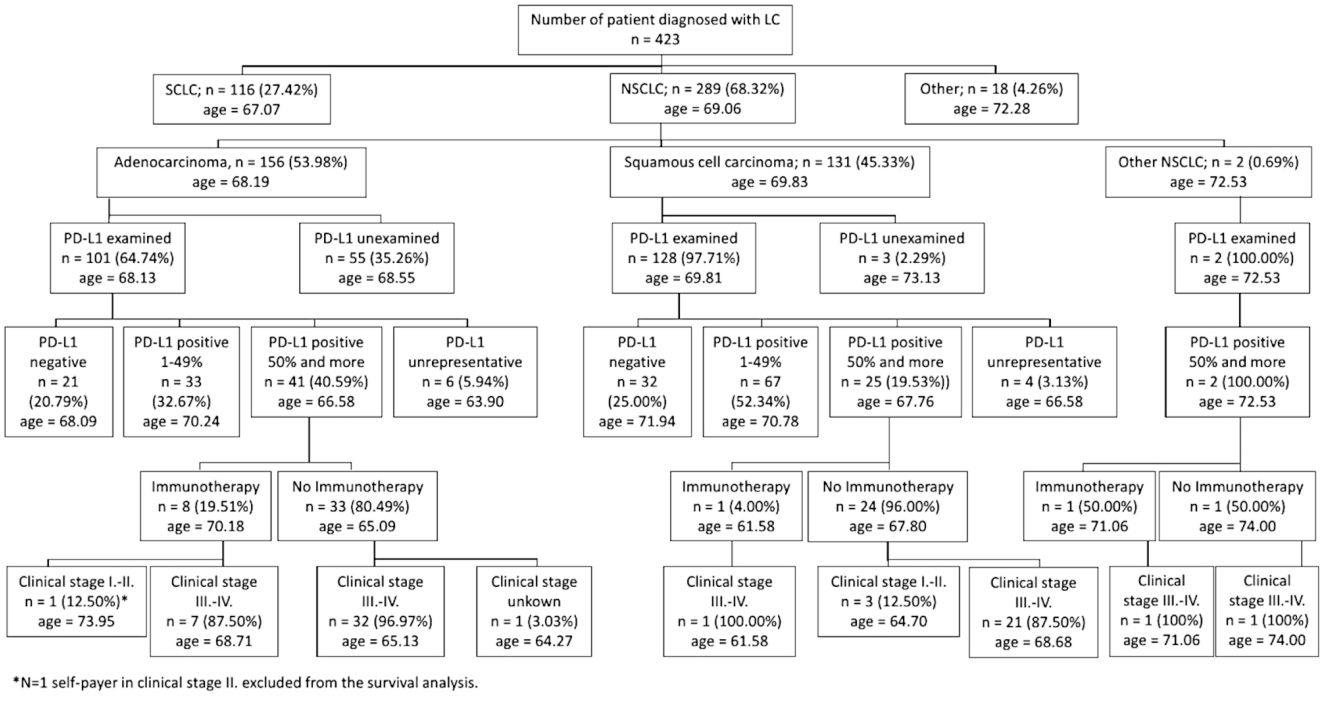

Figure 1. Basic characteristics of the whole patient cohort. *n=1 self-payer in clinical stage II excluded from the survival analysis.

Statistical analyses. Mortality predictions were made separately for males and females based on historical data from 1978 to 2022. Predictions for males were made using a model based on exponential smoothing (damped trend), for females a stochastic ARIMA (0;0;1) model was chosen.

A log-linear joinpoint regression model was used to analyze the trends of incidence and mortality over time (incidence hard data available for 1978–2014 and subsequently for 2017–2021, mortality hard data available for 1978–2022) using Joinpoint Regression Program software. At the 0.05 significance level for the Monte Carlo-based permutation test, assuming homoskedasticity and uncorrelated random errors, the number of breaks k in the respective data trend was determined using the grid search method under the condition $k \in (0;5)$ [23].

The basic characteristics of the cohort were analyzed by descriptive statistics and plotted in Figure 1. Continuous variable age at diagnosis was described using a median. All categorical variables were summarized as absolute and relative frequencies (percentages).

Primary as well as secondary outcomes included survival analysis of NSCLC (n=289) with right non-informative censoring. While the primary outcomes were focused on the survival of patients with TPS ≥50% treated with immunotherapy, the secondary outcomes dealt with the survival of SOC-treated patients depending on PD-L1 expression level. The starting point of the evaluation of survival time was defined as the date of the first diagnosis (histological verification of LC); the closing date was defined as the date of the patient's death or the date of the end of follow-up (September 1, 2023). Survival curves were generated using the method of Kaplan and Meier. The Log-rank test was chosen to test the null hypothesis that there is no difference between the populations in the probability of an event (=death) at any time point [24, 25]. In addition to overall survival, 1-year survival, and median survival time were reported. The breakpoint of PD-L1 expression was quantified using the proportion of patients at 1-year survival and the results of the log-rank test. All statistical tests were two-sided, and statistical significance was set at a p-value <0.05. Data were processed and analyzed using Microsoft 365 Excel (version 2311) and using libraries and packages in R (version 4.3.1-2023-06-16) [26].

In the analysis of each parameter, only patients with a record were included.

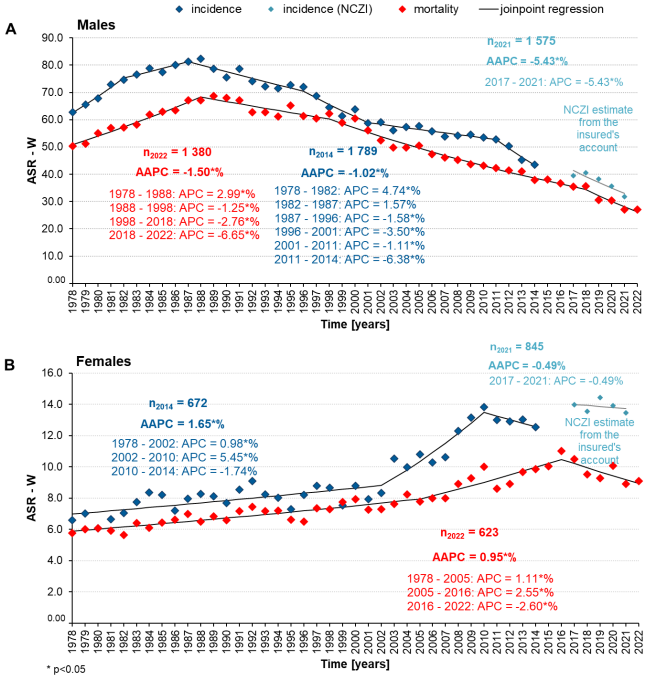

Figure 2. Incidence and mortality trends in LC patients between 1978–2022. A) Incidence and mortality trends in male LC patients between 1978–2022. B) Incidence and mortality trends in female LC patients between 1978–2022. Abbreviations: APC-annual percent change; AAPC-average annual percent change

Results

Descriptive epidemiology. According to the joinpoint regression model based on the data and predictions from National Health Information Center (NCZI) and NOR, the ASR-W incidence in men in the Slovak Republic declined statistically significantly between 1978 and 2014, with an average annual decrease of –1.02% (p<0.05; AAPC-average annual percent change; Figure 2A). ASR-W values of the NCZI estimates added to the NOR data for the period 2017–2021 decreased statistically significantly by –5.43% (p<0.05) (AAPC). ASR-W incidence in women increased statistically significantly throughout the period of 1978–2014 with an average annual increase of 1.65% (p<0.05; AAPC; Figure 2B). ASR-W values of the NCZI estimates for the period 2017–2021 decreased statistically insignificantly by –0.49% (p>0.05; AAPC).

ASR-W mortality in men declined statistically significantly to –1.50% (p<0.05; AAPC) between 1978 and 2022 (Figure 2A). ASR-W mortality due to LC in women had a statistically significant annual increasing trend of 0.95% (p<0.05; AAPC; Figure 2B).

Basic characteristics of the population. In 2020 and 2021, n=423 patients have been diagnosed with LC. Two hundred eighty-nine of them (68.32%) were histologically classified as NSCLC and met inclusion and exclusion criteria (Figure 1). The basic characteristics of the patients are summarized in Table 1. From the NSCLC group, adenocarcinomas were most prevalent (53.98%). In males, squamous cell carcinomas occurred more often than adenocarcinomas (54.40% and 45.08%, respectively), whereas in females, adenocarcinomas clearly dominated (71.88% vs. 27.08%, respectively). With immunotherapy were treated 19.51% of TPS≥50% of adenocarcinoma patients (n=8) and 4.00% of squamous cell carcinoma patients (n=1; Figure 1).

In general, patients with squamous cell carcinoma showed better 1-year survival than patients with adenocarcinoma (38.17%; 95% CI 30.69–47.46; vs. 28.20%; 95% CI 22.00–36.20; Table 2). Comparing PD-L1 expression levels, the worst survival in NSCLC males was obtained in patients with TPS=1–49% (29.58%; 95% CI 20.66–42.35) compared to males with TPS≥50% and TPS<1% (36.73%; 95% CI 25.44–53.05; and 37.14%; 95% CI 24.14–57.15; respectively). In NSCLC females, the TPS≥50% showed the best survival (47.40%; 95% CI 29.50–76.10). As expected, a comparison of 1-year survival according to the clinical stage showed the worst survival in patients in stage IV. The median survival of squamous cell carcinoma patients was longer than of adenocarcinoma patients (8.04 months vs. 6.00). Median survival in TPS≥50% females was longer than in TPS=1–49% and TPS<1% (11.40 months vs. 6.84 and 7.08 months, respectively), in males, the median survival of TPS≥50% and TPS=1–49% was similar (7.92 and 7.80 months, respectively; Table 2).

Effect of immunotherapy on survival. At the time of our study, in the Slovak Republic pembrolizumab was available and covered by health insurance as the first-line treatment of PD-L1 positive patients with metastatic NSCLC in clinical stage III and IV with TPS≥50%. In our study, 10 NSCLC patients were treated with immunotherapy: n=8 with adenocarcinoma, n=1 with squamous cell carcinoma, and n=1 with adenosquamous carcinoma (Figure 1). From n=8 adenocarcinoma patients, n=1 was a self-payer in clinical stage II (the rest of the patients were in clinical stage III and IV) and for this reason, was disclosed from the analysis. The comparison of survival of immunotherapy-treated stage III and IV NSCLC patients (n=9) with stage III and IV NSCLC patients treated with SOC (n=54) showed a significant difference in overall survival in favor of patients with immunotherapy (p=0.026; Figure 3). The comparison of immunotherapy-treated (n=7) and SOC-treated (n=32) adenocarcinoma patient's stage III and IV showed similar results (p=0.046; Figure 4). This kind of comparison was not possible in patients with squamous cell carcinoma or other types of NSCLC, because of the low number of immunotherapies-treated patients.

Breaking point of PD-L1 expression. The secondary outcome of our study was to evaluate the relationship between the PD-L1 expression level and survival in

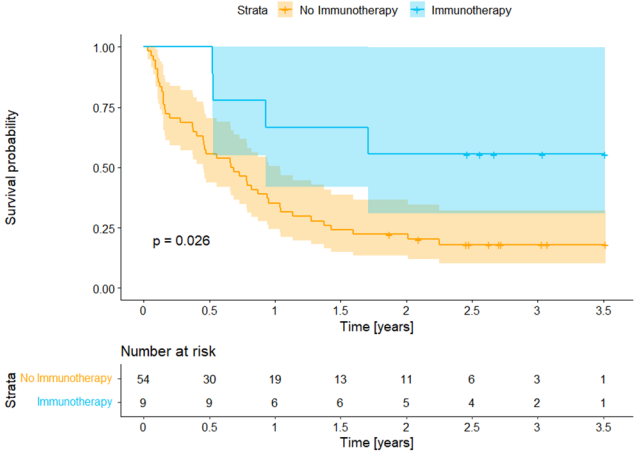

Figure 3. The comparison of survival of immunotherapy and SOC-treated patients. The comparison of survival of immunotherapy stage III and IV. NSCLC patients (n=9) with stage III and IV NSCLC patients treated with SOC (n=54).

Table 1. Basic characteristics of the patient cohort.

Patient	Male	Female	Total
Number of NSCLC patients	193 (66.78%)	96 (33.22%)	289 (100%)
ICD-10 subcategory			
adenocarcinoma	87 (45.08%)	69 (71.88%)	156 (53.98%)
squamous cell carcinoma	105 (54.40%)	26 (27.08%)	131 (45.33%)
other NSCLC	1 (0.52%)	1 (1.04%)	2 (0.69%)
PD-L1 expression in NSCLC			
examined	163 (84.46%)	68 (70.83%)	231 (79.93%)
unexamined	30 (15.54%)	28 (29.17%)	58 (20.07%)
PD-L1 expression examined	n=163	n=68	n=231
positive (TPS 1–49%)	71 (43.56%)	29 (42.65%)	100 (43.29%)
positive (TPS ≥50%)	49 (30.06%)	19 (27.94%)	68 (29.44%)
negative (TPS <1%)	35 (21.47%)	18 (26.47%)	53 (22.94%)
unrepresentative	8 (4.91%)	2 (2.94%)	10 (4.33%)
Clinical stage in NSCLC	n=193	n=96	n=289
stage I	2 (1.04%)	4 (4.17%)	6 (2.08%)
stage II	11 (5.70%)	5 (5.21%)	16 (5.54%)
stage III	68 (35.23%)	24 (25.00%)	92 (31.83%)
stage IV	108 (55.96%)	62 (64.58%)	170 (58.82%)
unknown	4 (2.07%)	1 (1.04%)	5 (1.73%)

SOC-treated patients. We performed the analysis on several groups of patients. At first, we analyzed the whole NSCLC population, females with NSCLC and males with NSCLC. Then we performed the same analysis on patients with adenocarcinoma (females, males, whole population) and squamous cell carcinoma (females, males, whole population). We graded the selected group of patients according to the level of PD-L1 expression and to each interval we assigned the observed survival of patients with PD-L1 expression within and exceeding the interval. Then, we compared the differences in 1-year survival in both groups of patients. In females with NSCLC (n=62), we identified a statistically significant difference in 1-year survival (for the entire 1-year period) at TPS 1–20% (Table 3). In this interval, there was a significant difference in survival during the 1-year period after diagnosis (p=0.0453). To look at the differences in patients' survival at the 1-year time point, we also performed a comparison using a color scale from dark green (100% observed survival) to dark red (0% observed survival). We looked for PD-L1 expression intervals with the greatest difference in color intensity between the proportions of patients surviving 1 year. The greatest difference was

Table 2. 1-year survival and median survival time depending on histological type, PD-L1 expression level, and clinical stage. In 1-year survival, the number of patients at the end of the 1st year is marked as n.

Patient	Male	Female	Total
1-year survival (%) (95% CI); NSCLC n (end of the 1st year)	**31.61 (25.68–38.90); n=61**	**36.46 (28.00–47.48); n=35**	**33.22 (28.21–39.12); n=96**
ICD-10 subcategory			
adenocarcinoma	25.29 (17.62–36.29); n=22	31.88 (22.58–45.01); n=22	28.20 (22.00–36.20); n=44
squamous cell carcinoma	36.19 (28.07–46.65); n=38	46.15 (30.47–69.91); n=12	38.17 (30.69–47.46); n=50
other NSCLC	*	*	*
PD-L1 expression			
examined	33.70 (27.20–41.80); n=55	42.60 (32.40–56.20); n=29	36.36 (30.66–43.13); n=84
unexamined	20.00 (9.78–40.91); n=6	21.43 (10.54–43.55); n=6	20.69 (12.50–34.24); n=12
PD-L1 expression examined			
positive (TPS 1-49%)	29.58 (20.66–42.35); n=21	41.38 (26.83–63.81); n=12	33.00 (25.00–43.60); n=33
positive (TPS ≥ 50%)	36.73 (25.44–53.05); n=18	47.40 (29.50–76.10); n=9	39.71 (29.62–53.22); n=27
negative (TPS < 1%)	37.14 (24.14–57.15); n=13	38.90 (21.80–69.40); n=7	37.74 (26.70–53.33); n=20
unrepresentative	*	*	*
Clinical stage			
stage I	100.00 (100.00 –100.00); n=2	75.00 (42.60–100.00); n=3	83.30 (58.30–100.00); n=5
stage II	36.40 (16.60–79.50); n=4	60.00 (29.30–100.00); n=3	43.80 (25.10–76.30); n=7
stage III	45.59 (35.16–59.10); n=31	62.50 (45.85–85.21); n=15	50.00 (40.76–61.34); n=46
stage IV	22.20 (15.60–31.60); n=24	20.97 (12.93–34.00); n=13	21.76 (16.37–28.94); n=37
unknown	*	*	*
Median survival time NSCLC (months)	**5.88**	**7.68**	**6.48**
ICD-10 subcategory			
adenocarcinoma	4.56	7.56	6.00
squamous cell carcinoma	7.92	11.04	8.04
other NSCLC	*	*	*
PD-L1 expression			
examined	7.80	10.32	7.92
unexamined	2.28	5.40	4.08
PD-L1 expression examined			
positive (TPS 1 - 49%)	7.80	6.84	7.32
positive (TPS ≥ 50%)	7.92	11.40	9.48
negative (TPS < 1%)	6.12	7.08	6.60
unrepresentative	*	*	*
Clinical stage			
stage I	18.00	26.16	20.16
stage II	10.08	16.20	10.08
stage III	10.56	20.40	11.76
stage IV	4.20	5.76	4.56
unknown	*	*	*

Note: *excluded from survival analysis

again at TPS 1–20%, which is the same breaking point as in the previous analysis (Table 3). At this level, 57.14% of patients with a TPS 1–20% survived at least 1 year vs. 26.09% of patients with higher PD-L1 expression. In males with NSCLC (n=149), we obtained different results. We identified statistically significant differences in 1-year survival (for the entire 1-year period) at TPS intervals between 1–70% and 1–90% (Supplementary Table S1). The analysis of the whole NSCLC group (n=211) didn't bring significant results (results not shown).

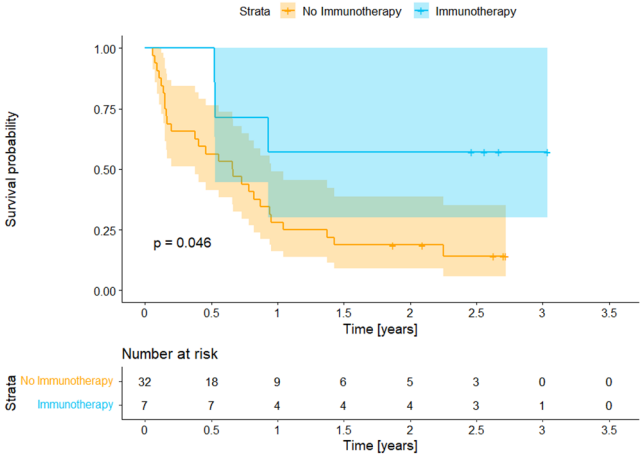

Figure 4. The comparison of survival of immunotherapy and SOC-treated adenocarcinoma patients. The comparison of survival of immunotherapy-treated stage III and IV adenocarcinoma patients (n=7) with stage III and IV adenocarcinoma patients treated with SOC (n=32).

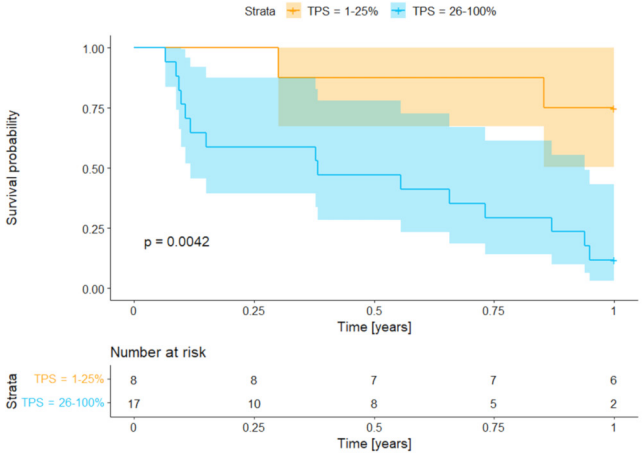

Figure 5. The comparison of survival of SOC-treated females with adenocarcinoma depending on TPS level. The comparison of survival of SOC-treated females with adenocarcinoma with TPS 1–25% and TPS 26–100%.

Table 3. Relationship between the PD-L1 expression level and survival in SOC-treated NSCLC females (n=62). Color scale: dark green=100% observed survival; dark red=0% observed survival; statistically significant p-values are in bold; the number of patients at the end of the 1st year is marked as n

TPS interval	1-year survival (%)				p-value (Log-rank test for the entire 1-year period)
	Start point		Endpoint (at the end of the 1st year)		
	Number of patients with TPS within the interval	Number of patients with TPS exceeding the interval	% of patients with TPS within the interval	% of patients with TPS exceeding the interval	
0%	18	44	38.89% (n=7)	40.91% (n=18)	0.9158
1–2%	5	39	40.00% (n=2)	41.03% (n=16)	0.8108
1–3%	6	38	33.33% (n=2)	42.11% (n=16)	0.3915
1–4%	8	36	50.00% (n=4)	38.89% (n=14)	0.8224
1–5%	12	32	50.00% (n=6)	37.50% (n=12)	0.4552
1–10%	17	27	58.82% (n=10)	29.63% (n=8)	0.0688
1–15%	19	25	57.89% (n=11)	28.00% (n=7)	0.0597
1–20%	21	23	57.14% (n=12)	26.09% (n=6)	**0.0453**
1–25%	22	22	54.55% (n=12)	27.27% (n=6)	0.0672
1–30%	27	17	44.44% (n=12)	35.29% (n=6)	0.9576
1–35%	27	17	44.44% (n=12)	35.29% (n=6)	0.9576
1–40%	29	15	41.38% (n=12)	40.00% (n=6)	0.6165
1–45%	29	15	41.38% (n=12)	40.00% (n=6)	0.6165
1–50%	29	15	41.38% (n=12)	40.00% (n=6)	0.6165
1–55%	31	13	41.94% (n=13)	38.46% (n=5)	0.8039
1–60%	31	13	41.94% (n=13)	38.46% (n=5)	0.8039
1–65%	31	13	41.94% (n=13)	38.46% (n=5)	0.8039
1–70%	31	13	41.94% (n=13)	38.46% (n=5)	0.8039
1–80%	32	12	40.63% (n=13)	41.67% (n=5)	0.6706
1–85%	32	12	40.63% (n=13)	41.67% (n=5)	0.6706
1–90%	38	6	39.47% (n=15)	50.00% (n=3)	0.4873
1–100%	44	-	40.91% (n=18)	–	–

Table 4. Relationship between the PD-L1 expression level and survival in SOC-treated females with adenocarcinoma (n=36). Color scale: dark green=100% observed survival; dark red=0% observed survival; statistically significant p-values are in bold; the number of patients at the end of the 1st year is marked as n

TPS interval	1-year survival (%)				p-value (Log-rank test for the entire 1-year period)
	Start point		Endpoint (at the end of the 1st year)		
	Number of patients with TPS within the interval	Number of patients with TPS exceeding the interval	% of patients with TPS within the interval	% of patients with TPS exceeding the interval	
0%	11	25	36.36% (n=4)	32.00% (n=8)	0.8432
1–2%	1	24	100.00% (n=1)	29.17% (n=7)	0.2769
1–3%	1	24	100.00% (n=1)	29.17% (n=7)	0.2769
1–4%	2	23	100.00% (n=2)	26.09% (n=6)	0.1095
1–5%	3	22	66.67% (n=2)	27.27% (n=6)	0.2022
1–10%	7	18	71.43% (n=5)	16.67% (n=3)	**0.0189**
1–15%	7	18	71.43% (n=5)	16.67% (n=3)	**0.0189**
1–20%	8	17	75.00% (n=6)	11.76% (n=2)	**0.0042**
1–25%	8	17	75.00% (n=6)	11.76% (n=2)	**0.0042**
1–30%	12	13	50.00% (n=6)	15.38% (n=2)	0.2643
1–35%	12	13	50.00% (n=6)	15.38% (n=2)	0.2643
1–40%	14	11	42.86% (n=6)	18.18% (n=2)	0.6446
1–45%	14	11	42.86% (n=6)	18.18% (n=2)	0.6446
1–50%	14	11	42.86% (n=6)	18.18% (n=2)	0.6446
1–55%	15	10	40.00% (n=6)	20.00% (n=2)	0.6448
1–60%	15	10	40.00% (n=6)	20.00% (n=2)	0.6448
1–65%	15	10	40.00% (n=6)	20.00% (n=2)	0.6448
1–70%	15	10	40.00% (n=6)	20.00% (n=2)	0.6448
1–80%	16	9	37.50% (n=6)	22.22% (n=2)	0.7761
1–85%	16	9	37.50% (n=6)	22.22% (n=2)	0.7761
1–90%	21	4	33.33% (n=7)	25.00% (n=1)	0.9922
1–100%	25	–	32.00% (n=8)	–	–

In females with adenocarcinoma (n=36), we again identified statistically significant differences in 1-year survival at the TPS intervals between 1–10% and 1–25% (Table 4). The TPS intervals between 1–20% and 1–25% with the lowest p-value (p=0.0042) can be seen as a breaking point (Table 4, Figure 5). By analyzing the differences in color intensity, we identified the greatest difference again at TPS intervals of 1–20% or 1–25%. At this level, 75.00% of patients with a TPS inside these intervals survived at least 1 year vs. 11.76% of patients with higher PD-L1 expression. The TPS value can't be further specified because there were no patients with TPS between 20% and 25%. Analyses in males and in the total population with adenocarcinoma, and in patients with squamous cell carcinoma (females, males, total population) didn't show significant results (results not shown).

Discussion

Trends in incidence and mortality of males and females with LC in the Slovak Republic differ significantly. Although incidence and mortality in males is significantly higher than in females, males' incidence and mortality shows a statistically significant average annual decrease (Figure 2A). On the contrary, the incidence and survival in females with LC show increasing trends with a hint of a plateau in recent years (Figure 2B), which is consistent with the results of other studies [7, 27].

According to Pleško et al. [9], during the period of 1978–1995, n=29,430 microscopically confirmed cases of LC in the Slovak Republic were identified. Of them, 54.3% were squamous cell carcinomas and 13.9% adenocarcinomas. According to the predictions of NOR, there were n=6,188 newly diagnosed patients during the period 2020–2021 in Slovakia [18]. Our study comprises n=423 patients from the Nitra district diagnosed with LC during this period, which according to these predictions represents 6.84% of all newly diagnosed Slovakian LC patients. From this number, 30.97% were squamous cell carcinomas and 36.88% adenocarcinomas. Although our sample is smaller, it indicates an increase in adenocarcinomas and a decrease in squamous cell carcinomas, which is a trend visible in many countries approximately from the 1990s [27, 28]. This trend may be related to the increased incidence of LC in females, who have higher rates of adenocarcinoma relative to squamous cell carcinoma [7, 27]. The increased incidence of LC in females is evident also in Slovak LC patients [29]. In 2020–2021, adenocarcinomas clearly dominated in females: 71.88% of NSCLCs and 51.49% of all females with LC. Squamous cell carcinomas

represented 27.08% of NSCLCs and 19.40% of all females with LC. During the period of 1978–1995, the proportion of adenocarcinomas and squamous cell carcinomas in females was almost equal: 32.2% and 31.9% of all females with LC respectively [9]. The proportion of adenocarcinomas rose also in males. During 1978–1995, the proportion of adenocarcinomas was 11.7% vs. 57.1% squamous cell carcinomas. In 2020–2021, the difference decreased markedly: 30.10% vs. 36.33% of all male LC patients.

An improvement in survival of LC patients is evident in many countries [30–34]. The 1-year survival rate of the whole patient cohort in our study was 33.22 % (31.61% in males and 36.46% in females). According to an Annual report of NCZI from 2006 [35], the 1-year survival of male patients with lung and trachea cancer was 33.0% in 1980–1984 and 32.6% in 2000–2004. In females, 1-year survival was 34.8% and 40.0%, respectively. So, despite the improvements in health care and the availability of modern treatments, we do not see an increase in the 1-year survival of LC patients in our study.

Since the proportion of adenocarcinomas is markedly increasing, we focused on them in our analyses. We had a group of n=41 patients with TPS ≥50%, and n=7 of them (in clinical stage III and IV) were treated with immunotherapy. A comparison of the overall survival of immunotherapy-treated patients and patients treated with SOC (n=32) showed significantly better survival (p=0.046) in immunotherapy-treated patients (Figure 4). This trend is emphasized by the fact that adenocarcinoma patients treated with immunotherapy are older (median age 70.18 years) compared with the SOC-treated patients (median age 65.09 years) and younger age is associated with reduced mortality in NSCLC patients [36, 37]. Moreover, n=6 of the patients treated with SOC were ALK or ROS1 positive and treated with targeted therapy, which is a group with a good prognosis [38]. A comparison of the overall survival of the whole cohort of immunotherapy-treated NSCLC patients (n=9) with NSCLC patients treated with SOC also showed significantly better 3-year survival in patients treated with immunotherapy (Figure 3). This result is in accordance with the outcomes of clinical trials of immunotherapeutic agents [39], but we have to take into account the selection bias of our cohort, where the patients treated with immunotherapy were selected by the health insurance companies as patients who are expected to benefit most from the immunotherapy treatment. On the other hand, in the group treated with SOC are patients, who did not obtain permission for immunotherapy, patients with impaired performance status (PS2 or greater), patients with brain metastases treated with corticosteroids, patients with active autoimmune diseases, but also target therapy treated patients with favorable prognosis. A comparison of our results with other real-world data studies is complicated since most of them analyze only the outcomes of immunotherapy-treated patients [40, 41, 423]. A study based on data from the Cancer Registry of Norway from the period 2010–2020 investigated the survival development in stage IV NSCLC adenocarcinoma patients, with an emphasis on changes specifically after 2016, which was the time point of PD-1/PD-L1 inhibitors introduction [44]. Results of the study showed that 1-year and 2-year relative survival of patients with stage IV adenocarcinomas increased for both sexes with the steepest survival increase after 2016. A study based on data from the Czech TULUNG Registry compared survival outcomes in NSCLC patients treated with modern-era drugs (including immunotherapy) during the periods 2011–12 and 2015–16 [45]. The 2-year survival probability of stage IIIB and IV NSCLC patients doubled in 2015–16 (for both adenocarcinoma and squamous cell carcinoma). This improvement might be affected by the increased availability of modern treatments, including immunotherapy.

PD-L1 expression level is considered an important biomarker in NSCLC patients, even if the results of the studies are inconsistent [46]. Although positive PD-L1 expression is associated with poorer prognosis in the advanced stage [16] patients with higher PD-L1 expression are more likely to respond to ICI treatment. Usually, TPS cut-off values of 1% (nivolumab) or 50% (pembrolizumab) are used. One of the aims of our study was to investigate the effect of PD-L1 expression levels on survival in different subgroups: patients with NSCLC, patients with adenocarcinoma, and patients with squamous cell carcinoma. The results in females with NSCLC and females with adenocarcinomas indicate that the negative effect of PD-L1 expression level on females' survival might manifest already at a TPS level of 20–25%. On the contrary, in males with NSCLC, we saw the negative effect at a much higher level: 70–90%, which might suggest a different effect of PD-L1 expression level on survival for males and females. Definitely, more research on this topic is needed, but this result might be a basis for the discussion on personalizing the conditions for immunotherapy treatment.

Our study has some limitations. As a single-center study, it doesn't include nationally representative data, but it represents data from a medium-sized metropolitan area of Slovakia. The proportion of PD-L1 tested patients might be different compared to other centers. The prescribed immunotherapy also might differ from custom treatment in other centers but on the other hand, it represents only one type of ICI. The decision-making process of the health insurance companies may have caused a selection bias. During 2020–2021 immunotherapy was available only upon permission from a health insurance company and not all patients, who met the indication criteria, were treated. We have also noticed a high diversity of the SOC treatment group. This cohort contained patients with low-performance status (WHO PS2 or greater) or patients with brain metastases requiring corticosteroids as well as patients with normal PS or limited metastatic disease.

Our study offers unique insight into Slovakia's LC patient population, including characteristics of histology, immunology, imaging, and clinical parameters. The histological results confirm the trend of increasing incidence of adenocarcinomas in LC patients. Analysis of the effects of

immunotherapy treatment enables the comparison between treated and untreated patients in real-world conditions. The determination of different PD-L1 expression breaking points in males and females with NSCLC is a solid starting point for more research on the diverse cut-off values for immunotherapy in patients according to their sex, age, or histological type of tumor.

Supplementary information is available in the online version of the paper.

References

[1] FERLAY J, ERVIK M, LAM F, LAVERSANNE M, COLOMBET M et al. Global Cancer Observatory: Cancer Today (version 1). Lyon, France: International Agency for Research on Cancer 2024. https://gco.iarc.who.int/today [As accessed on March 8, 2024].

[2] GANTI AK, KLEIN AB, COTARLA I, SEAL B, CHOU E. Update of incidence, prevalence, survival, and initial treatment in patients with non–small cell lung cancer in the US. JAMA Oncol 2021; 7: 1–9. https://doi.org/10.1001/jamaoncol.2021.4932

[3] WALTERS S, MARINGE C, COLEMAN MP. Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004–2007. Thorax 2013; 68: 551–564. https://doi.org/10.1136/thoraxjnl-2012-202297

[4] LIN HT, LIU FC, WU CY, KUO CF, LAN WC et al. Epidemiology and survival outcomes of lung cancer: A population-based study. Biomed Res Int 2019; 2019: 8148156. https://doi.org/10.1155/2019/8148156

[5] LIM SL, JIA Z, LU Y, ZHANG H, NG CT et al. Metabolic signatures of four major histological types of lung cancer cells. Metabolomics 2018; 14: article 118. https://doi.org/10.1007/s11306-018-1417-x

[6] JANSSEN-HEIJNEN MLG, COEBERGH JWW. The changing epidemiology of lung cancer in Europe. Lung Cancer 2003; 41: 245–258. https://doi.org/10.1016/s0169-5002(03)00230-7

[7] YOULDEN DR, CRAMB SM, BAADE PD. The international epidemiology of lung cancer: geographical distribution and secular trends. J Thorac Oncol 2008; 3: 819–831. https://doi.org/10.1097/JTO.0b013e31818020eb

[8] FRANCISCI S, MINICOZZI P, PIERANNUNZIO D, ARDANAZ E, EBERLE A et al. Survival patterns in lung and pleural cancer in Europe 1999–2007: Results from the EUROCARE-5 study. Eur J Cancer 2015; 51: 2242–2253. https://doi.org/10.1016/j.ejca.2015.07.033

[9] PLESKO I, SEVERI G, OBSITNÍKOVÁ A, BOYLE P, KUBÍK A. Lung cancer incidence rates by histologic type: an example of trends in Eastern Europe--Slovakia 1978–95. Neoplasma 2001; 48: 247–253.

[10] DOROSHOW DB, SANMAMED MF, HASTINGS K, POLITI K, RIMM DL et al. Immunotherapy in non–small cell lung cancer: facts and hopes. Clin Cancer Res 2019; 25: 4592–4602. https://doi.org/10.1158/1078-0432.CCR-18-1538

[11] BRODY R, ZHANG Y, BALLAS M, SIDDIQUI MK, GUPTA P et al. PD-L1 expression in advanced NSCLC: Insights into risk stratification and treatment selection from a systematic literature review. Lung Cancer Amst Neth 2017; 112: 200–215. https://doi.org/10.1016/j.lungcan.2017.08.005

[12] ISHIDA Y, AGATA Y, SHIBAHARA K, HONJO T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J 1992; 11: 3887–3895. https://doi.org/10.1002/j.1460-2075.1992.tb05481.x

[13] POSTOW MA, CALLAHAN MK, WOLCHOK JD. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015; 33: 1974–1982. https://doi.org/10.1200/JCO.2014.59.4358

[14] MEHDIZADEH S, BAYATIPOOR H, PASHANGZADEH S, JAFARPOUR R, SHOJAEI Z et al. Immune checkpoints and cancer development: therapeutic implications and future directions. Pathol Res Pract 2021; 223: 153485. https://doi.org/10.1016/j.prp.2021.153485

[15] PARDOLL DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012; 12: 252–264. https://doi.org/10.1038/nrc3239

[16] ZHAO Y, SHI F, ZHOU Q, LI Y, WU J et al. Prognostic significance of PD-L1 in advanced non-small cell lung carcinoma. Medicine (Baltimore) 2020; 99: e23172. https://doi.org/10.1097/MD.0000000000023172

[17] [NATIONAL HEALTH INFORMATION CENTER] [Cancer incidence in the Slovak Republic] https://www.nczisk.sk/Statisticke_vystupy/Tematicke_statisticke_vystupy/Onkologia/Vystupy_NOR_SR/Pages/Incidencia-zhubnych-nadorov.aspx [As accessed on April 2, 2024]

[18] [NATIONAL HEALTH INFORMATION CENTER] [Cancer incidence estimates in the Slovak Republic] https://iszi.nczisk.sk/nor.sr/incidencia/odhad/sumarny-prehlad?filter={%22ukazovatel%22:%22abs%22,%22pohlavie%22:[%22M%22],%22rok-od%22:1997,%22rok-do%22:2030,%22diagnoza%22:[%22SPOLU%22]} [As accessed on March 3, 2024]

[19] [STATISTICAL OFFICE OF THE SLOVAK REPUBLIC] [Source work - causes of death, 2023]. https://slovak.statistics.sk/wps/portal/ext/themes/demography/population/indicators [As accessed on March 3, 2024]

[20] CHOWANIECOVÁ G, ONDRUŠ D. [Targeted treatment of non-small cell lung cancer-update] Onkológia (Bratisl) 2022; 17: 266–271. https://www.solen.sk/storage/file/article/ONKO_4_2022_final%20%E2%80%93%20Chowaniecova.pdf

[21] [STATISTICAL OFFICE OF THE SLOVAK REPUBLIC]. [The average state of the population. The number of permanent residents as of 30.6.2023]. http://www.statistics.sk/pls/elisw/MetaInfo.explorer?obj=30&cmd=go&s=1002&sso=2&so=7 [As accessed on April 2, 2024]

[22] PD-L1 IHC 22C3 PHARMDX NSCLC INTERPRETATION MANUAL – NSCLC. Dako Agilent Pathology Solutions. https://www.agilent.com/cs/library/usermanuals/public/29158_pd-l1-ihc-22C3-pharmdx-nsclc-interpretation-manual.pdf [As accessed on May 2, 2024]

[23] KIM, HJ, FAY MP, FEUER ES, MIDTHUNE DN. Permutation Tests for Joinpoint Regression with Applications to Cancer Rates. Stat Med 2000; 19: 335–351. (correction: 2001; 20: 655). https://doi.org/10.1002/(sici)1097-0258(20000215)19:3<335::aid-sim336>3.0.co;2-z

[24] KLEINBAUM DG, KLEIN M. Survival analysis a self-learning text. Springer 2012; ISBN 978-1-4419-6645-2

[25] BENCKO V, HRACH K, MALÝ M, PIKHART H, REISSIGOVÁ J et al. [Biomedical Statistics III, Statistical Methods in Epidemiology. (1)], Nakladatelství Karolinum, Praha ISBN 80-246-0763-8. 2003. p. 236.

[26] TEAM RC. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2023. https://www.R-project.org/ [As accessed on February 8, 2024]

[27] LORTET-TIEULENT J, SOERJOMATARAM I, FERLAY J, RUTHERFORD M, WEIDERPASS E et al. International trends in lung cancer incidence by histological subtype: Adenocarcinoma stabilizing in men but still increasing in women. Lung Cancer 2014; 84: 13–22. https://doi.org/10.1016/j.lungcan.2014.01.009

[28] BARTA JA, POWELL CA, WISNIVESKY JP. Global epidemiology of lung cancer. Ann Glob Health 2019; 85: 8. https://doi.org/10.5334/aogh.2419

[29] JUSKANIC D, SANDOR F, DENKOVA L, JUHOS P, JANIK M et al. Lung cancer screening initiative in Slovakia: Guidelines of screening implementation. Bratisl Lek Listy 2023; 124: 109–115. https://doi.org/10.4149/BLL_2023_016

[30] FRISONE D, SANDOVAL J, FRIEDLAENDER A, OLIVIER T, ADDEO A. Trends in incidence and mortality of lung cancer in Switzerland: Possible explanations and open questions. Cancer Epidemiol 2022; 80: 102232. https://doi.org/10.1016/j.canep.2022.102232

[31] SØRENSEN JB, EKMAN S, BRUSTUGUN OT, HORVAT P, PATEL D et al. Evolution of overall survival (OS) in patients (pts) with incident NSCLC in Denmark and Sweden: A SCAN-LEAF study analysis from the I-O Optimise initiative. Ann Oncol 2019; 30: ii16–ii17. https://doi.org/10.1093/annonc/mdz070.004

[32] KOSKINEN A, HEMMINKI O, FÖRSTI A, HEMMINKI K. Incidence and survival in laryngeal and lung cancers in Finland and Sweden through a half century. PLoS One 2022; 17: e0268922. https://doi.org/10.1371/journal.pone.0268922

[33] HU S, ZHANG W, GUO Q, YE J, ZHANG D et al. Prognosis and Survival Analysis of 922,317 Lung Cancer Patients from the US Based on the Most Recent Data from the SEER Database (April 15, 2021). Int J Gen Med 2021; 14: 9567–9588. https://doi.org/10.2147/IJGM.S338250

[34] TSAI HC, HUANG JY, HSIEH MY, WANG BY. Survival of lung cancer patients by histopathology in Taiwan from 2010 to 2016: A nationwide study. J Clin Med 2022; 11: 5503. https://doi.org/10.3390/jcm11195503

[35] [NATIONAL HEALTH INFORMATION CENTER] [Annual report of NCZI – Incidence of Malignant Tumors in the Slovak Republic 2006] https://data.nczisk.sk/statisticke_vystupy/Onkologia/incidencia_zhubnych_nadorov_2006.pdf [As accessed on April 5, 2024]

[36] XIA W, WANG A, JIN M, MAO Q, XIA W et al. Young age increases risk for lymph node positivity but decreases risk for non-small cell lung cancer death. Cancer Manag Res 2018; 10: 41–48. https://doi.org/10.2147/CMAR.S152017

[37] RICH AL, KHAKWANI A, FREE CM, TATA LJ, STANLEY RA et al. Non-small cell lung cancer in young adults: presentation and survival in the English National Lung Cancer Audit. QJM 2015;108: 891–897. https://doi.org/10.1093/qjmed/hcv052

[38] GÁLFFY G, MORÓCZ É, KOROMPAY R, HÉCZ R, BUJDOSÓ R et al. Targeted therapeutic options in early and metastatic NSCLC-overview. Pathol Oncol Res 2024; 30: 1611715. https://doi.org/10.3389/pore.2024.1611715

[39] RECK M, RODRÍGUEZ-ABREU D, ROBINSON AG, HUI R, CSŐSZI T et al. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non-small-cell lung cancer with PD-L1 tumor proportion score ≥ 50. J Clin Oncol 2021; 39: 2339–2349. https://doi.org/10.1200/JCO.21.00174

[40] CHOUAID C, THOMAS M, DEBIEUVRE D, DURAND-ZALESKI I, ZACHARIAS S et al. Effectiveness of nivolumab in second-line and later in patients with advanced non-small cell lung cancer in real-life practice in France and Germany: Analysis of the ESME-. AMLC and CRISP Cohorts. Cancers (Basel) 2022; 14: 6148. https://doi.org/10.3390/cancers14246148

[41] CRINÒ L, BIDOLI P, DELMONTE A, GROSSI F, DE MARINIS F et al. Italian cohort of nivolumab expanded access program in squamous non-small cell lung cancer: Results from a real-world population. Oncologist 2019; 24: e1165–e1171. https://doi.org/10.1634/theoncologist.2018-0737

[42] MENCOBONI M, CEPPI M, BRUZZONE M, TAVEGGIA P, CAVO A et al. Effectiveness and safety of immune checkpoint inhibitors for patients with advanced non small-cell lung cancer in real-world: review and meta-analysis. Cancers (Basel) 2021; 13: 1388. https://doi.org/10.3390/cancers13061388

[43] IVANOVIĆ M, KNEZ L, HERZOG A, KOVAČEVIĆ M, CUFER T. Immunotherapy for metastatic non-small cell lung cancer: Real-world data from an academic Central and Eastern European Center. Oncologist 2021; 26: e2143–e2150. https://doi.org/10.1002/onco.13909

[44] BØRØ S, THORESEN S, HELLAND Å. Improvements in survival for patients with stage IV adenocarcinoma in the lung, diagnosed between 2010 – 2020. A population-based registry study from Norway. Front Oncol 2022; 12: 1017902. https://doi.org/10.3389/fonc.2022.1017902

[45] BRATOVA M, KARLINOVA B, SKRICKOVA J, PESEK M, KOLEK V et al. Non-small cell lung cancer as a chronic disease – A prospective study from the Czech TULUNG Registry. In Vivo 2020; 34: 369–379. https://doi.org/10.21873/invivo.11783

[46] CHA YJ, KIM HR, LEE CY, CHO BC, SHIM HS. Clinicopathological and prognostic significance of programmed cell death ligand-1 expression in lung adenocarcinoma and its relationship with p53 status. Lung Cancer 2016; 97: 73–80. https://doi.org/10.1016/j.lungcan.2016.05.001

https://doi.org/10.4149/neo_2024_240625N272

The real-world comparison of non-small cell lung cancer survival outcomes depending on immunotherapy treatment and PD-L1 expression level

Martina ONDRUŠOVÁ[1,2], Martin SUCHANSKÝ[1], Soňa VÁNDOR SVIDOVÁ[1], Gabriela CHOWANIECOVÁ[3], Bela MRIŇÁKOVÁ[4], Monika SEKEREŠOVÁ[5], Dominik JUSKANIČ[6,7], Dalibor ONDRUŠ[4,#,*], Michal ŠENITKO[8,9,#,*]

Supplementary Information

Supplementary Table S1. Relationship between the PD-L1 expression level and survival in SOC treated NSCLC males (n=149). Colour scale: dark green=100% observed survival; dark red=0% observed survival; statistically significant p-values are in bold; the number of patients at the end of the 1st year is marked as n

TPS interval	1-year survival (%)				p-value (Log-rank test for the entire 1-year period)
	Start point		End point (at the end of the 1st year)		
	Number of patients with TPS within the interval	Number of patients with TPS exceeding the interval	% of patients with TPS within the interval	% of patients with TPS exceeding the interval	
0%	35	114	37.14% (n=13)	31.58% (n=36)	0.6248
1–2%	13	101	38.46% (n=5)	30.69% (n=31)	0.8250
1–3%	18	96	38.89% (n=7)	30.21% (n=29)	0.5481
1–4%	19	95	36.84% (n=7)	30.53% (n=29)	0.6210
1–5%	33	81	30.30% (n=10)	32.10% (n=26)	0.8946
1–10%	39	75	28.21% (n=11)	33.33% (n=25)	0.5082
1–15%	46	68	28.26% (n=13)	33.82% (n=23)	0.4920
1–20%	56	58	25.00% (n=14)	37.93% (n=22)	0.0914
1–25%	58	56	27.59% (n=16)	35.71% (n=20)	0.2459
1–30%	61	53	26.23% (n=16)	37.74% (n=20)	0.1667
1–35%	64	50	26.56% (n=17)	38.00% (n=19)	0.1810
1–40%	70	44	28.57% (n=20)	36.36% (n=16)	0.5052
1–45%	71	43	29.58% (n=21)	34.88% (n=15)	0.6860
1–50%	72	42	30.56% (n=22)	33.33% (n=14)	0.8896
1–55%	73	41	31.51% (n=23)	31.71% (n=13)	0.8956
1–60%	80	34	32.50% (n=26)	29.41% (n=10)	0.4819
1–65%	82	32	32.93% (n=27)	28.13% (n=9)	0.3103
1–70%	89	25	34.83% (n=31)	20.00% (n=5)	**0.0396**
1–80%	97	17	34.02% (n=33)	17.65% (n=3)	**0.0189**
1–85%	99	15	34.34% (n=34)	13.33% (n=2)	**0.0057**
1–90%	106	8	33.96% (n=36)	0.00% (n=0)	**0.0009**
1–100%	114	–	31.58% (n=36)	–	–