

# Real-world PD-L1 testing, first-line therapy for advanced NSCLC, and first-line pembrolizumab monotherapy utilization and outcomes for metastatic NSCLC in the Czech Republic

Testování PD-L1 v reálné praxi, první linie léčby pokročilého NSCLC a výsledky a využití první linie léčby metastatického NSCLC pembrolizumabem v monoterapii v České republice

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## Summary

**Background:** This study aimed to describe real-world PD-L1 testing and first-line (1L) treatment patterns for advanced non-small cell lung cancer (NSCLC), and clinical outcomes for metastatic NSCLC after 1L pembrolizumab monotherapy became reimbursed in the Czech Republic (February 2019). **Patients and methods:** This descriptive noninterventional study drew on two Czech lung cancer registries. We examined PD-L1 testing patterns and results in the KELLY registry for samples submitted on/after 1-Feb-2019 from adult patients with advanced NSCLC. Using the TULUNG registry, we summarized 1L targeted therapies initiated on/after 1-Feb-2019 for advanced NSCLC, in addition to characteristics and outcomes for patients treated with 1L pembrolizumab monotherapy for metastatic NSCLC, PD-L1 tumor proportion score (TPS)  $\geq 50\%$ , and no known *EGFR/ALK* alterations. Real-world time on treatment (rwToT) and overall survival (OS) were determined using Kaplan-Meier curves. The data cutoff was 16-Sept-2021. **Results:** The percentage of NSCLC samples in the KELLY registry tested for PD-L1 expression increased from 70.5% in 2019 to 84.4% in 2021. Pembrolizumab monotherapy was the most common 1L targeted therapy in 2019–2021 for patients with advanced NSCLC and PD-L1 TPS  $\geq 50\%$  (N = 315), administered to 70–80% each year. Of 235 patients with metastatic NSCLC who re-

ceived 1L pembrolizumab monotherapy, median age was 69 years, 54% were men, 52% were current smokers, and 28% had squamous NSCLC. Median rwToT was 8.5 months (95% CI; 6.7–10.1), with 6- and 12-month on-treatment rates of 59% and 36%, respectively, for 199 patients with  $\geq 6$  months of follow-up. With added national registry mortality data, estimated median OS was 13.7 months (12.3–17.7); 6- and 12-month OS rates were 70% and 59%, respectively. **Conclusions:** The rates of PD-L1 testing increased from 2019 to 2021. Median OS among patients with metastatic NSCLC and PD-L1 TPS  $\geq 50\%$  treated with pembrolizumab was lower than in clinical trials, likely due to differences between real-world patients and trial participants in age, smoking status, performance status, and squamous histology.

### Key words

carcinoma – non-small-cell lung – Czech Republic – immunotherapy – pembrolizumab monotherapy – programmed death-ligand 1 – real-world data

### Souhrn

**Východiska:** Cílem této studie bylo popsat testování PD-L1 a schéma léčby první linie (1L) u pokročilého nemalobuněčného karcinomu plic (non-small cell lung cancer – NSCLC) a klinické výsledky u metastatického NSCLC v reálné praxi po zavedení úhrady monoterapie pembrolizumabem v České republice (únor 2019). **Pacienti a metody:** Tato deskriptivní neintervenci studie čerpala z dvou českých registrů plicních nádorů. Zkoumali jsme schéma testování PD-L1 a výsledky v registru KELLY u vzorků od dospělých pacientů s pokročilým NSCLC odeslaných 1. února 2019 nebo později. Pomocí registru TULUNG jsme shrnuli výsledky cílené léčby první linie u pokročilého NSCLC zahájené 1. února 2019 nebo později, kromě charakteristik a výsledků u pacientů léčených v první linii pembrolizumabem v monoterapii pro metastatický NSCLC se skóre nádorového podílu (tumor proportion score – TPS)  $\geq 50\%$  a bez známých alterací *EGFR/ALK*. Skutečná doba léčby (real-world time on treatment – rwToT) a celkové přežití (overall survival – OS) byly stanoveny pomocí Kaplan-Meierovy metody. Data byla shromážděna k 16. září 2021. **Výsledky:** Procento vzorků NSCLC v registru KELLY testovaných na expresi PD-L1 se zvýšilo ze 70,5 % v roce 2019 na 84,4 % v roce 2021. U pacientů s pokročilým NSCLC a PD-L1 TPS  $\geq 50\%$  ( $n = 315$ ) byla v letech 2019–2021 nejčastější cílenou léčbou první linie monoterapie pembrolizumabem, podávaná každoročně 70–80 % pacientů. Z 235 pacientů s metastatickým NSCLC, kteří byli v první linii léčení pembrolizumabem v monoterapii, byl medián věku 69 let, 54 % byli muži, 52 % byli aktuální kuřáci a 28 % mělo skvamózní NSCLC. Medián rwToT byl 8,5 měsíce (95% CI 6,7–10,1), přičemž OS po 6 a 12 měsících léčby u 199 pacientů bylo 59 % a 36 % při  $\geq 6$  měsících sledování. Po přidání údajů o úmrtnosti z národního registru byl odhadovaný medián OS 13,7 měsíce (12,3–17,7); po 6 a 12 měsících byla míra OS 70% a 59 %. **Závěry:** Míra testování PD-L1 se v letech 2019–2021 zvýšila. Medián OS u pacientů s metastatickým NSCLC a PD-L1 TPS  $\geq 50\%$  léčených pembrolizumabem byl nižší než v klinických studiích, pravděpodobně kvůli rozdílům mezi pacienty v reálné praxi a účastníky studií, a to z hlediska věku, kouření, výkonnostním stavu a skvamózní histologie.

### Klíčová slova

nemalobuněčný – karcinom plic – Česká republika – imunoterapie – pembrolizumab – monoterapie – ligand programované buněčné smrti 1 – data z reálné praxe

### Introduction

Lung cancer continues to be the most common cause of cancer death globally. Non-small cell lung cancer (NSCLC) accounts for about 80–85% of all lung cancers and has a 28% 5-year relative survival rate [1]. The age-standardized death rate for lung cancer is the highest in Europe compared with other continents, estimated in 2022 as 21.4 per 100,000 standard population, and varying widely by country. In the Czech Republic (Czechia), a central European country, the rate is 19.8, similar to the surrounding countries, namely, Austria (19.5), Germany (21.4), and Slovakia (19.3), and lower than in Poland (30.5) [2].

The diagnosis of NSCLC is most common at an unresectable advanced or metastatic stage of disease when the 5-year relative survival rate is only 9% [1]. The European Society of Medical

Oncology (ESMO) clinical practice guidelines for metastatic NSCLC provide targeted treatment algorithms for patients with specific molecular alterations, such as *ALK*, *ROS1*, or *EGFR* genomic alterations [3,4]. For patients with NSCLC without these alterations, the standard of care was platinum-based therapy until the treatment landscape shifted after the authorization of first-line (1L) immunotherapy for patients with metastatic NSCLC and programmed death-ligand 1 (PD-L1) tumor proportion score (TPS)  $\geq 50\%$  [4]. In 2016, results of the KEYNOTE-024 study, a randomized phase III trial investigating pembrolizumab monotherapy vs. platinum-based doublet chemotherapy regimens in patients with previously untreated metastatic NSCLC whose tumors expressed PD-L1 TPS  $\geq 50\%$  without *EGFR/ALK* alterations, showed pembrolizumab was superior to platinum chemotherapy for

both the primary endpoint of progression-free survival and the secondary endpoint of overall survival (OS) [5]. On the basis of results from this trial, pembrolizumab became the first immunotherapy approved by the European Medicines Agency (EMA) in January 2017 for the 1L treatment of metastatic NSCLC with PD-L1 TPS  $\geq 50\%$  and no *EGFR* mutations or *ALK* translocations [6]. Subsequently, the EMA approved pembrolizumab in combination with chemotherapy as 1L treatment for metastatic nonsquamous (September 2018) and squamous (March 2019) NSCLC, independent of PD-L1 expression [7,8].

In most European countries, patients with NSCLC were able to access pembrolizumab in 2017–2018. Accessibility was suboptimal in Central and Eastern European countries where initial access to pembrolizumab spanned from 2019 to 2020 [9]. In the Czech Republic,

eligible patients with NSCLC continued receiving platinum doublet therapy until pembrolizumab became accessible via public insurance reimbursement in 2019. For nonsquamous NSCLC in patients with PD-L1 TPS  $\geq$  50%, pembrolizumab was reimbursed in the 1L setting in combination with pemetrexed and platinum chemotherapy in March 2021.

Observational studies can complement findings from clinical trials by describing the implementation and effectiveness of new treatments once they become accessible to patients in real-world clinical settings. Real-world patient populations are more heterogeneous and often differ from clinical trial populations in terms of prognostic patient and clinical characteristics. The need for real-world observational research is especially relevant in Europe where the lung cancer survival rate shows high variation. Several data-rich registries are maintained for Czech patients with cancer. The TULUNG and KELLY registries are unique data sources providing the opportunity to study biomarker testing, treatment patterns, and associated clinical outcomes in routine clinical practice in central Europe [10,11].

This study aimed to describe real-world PD-L1 testing, treatment patterns, and clinical outcomes in patients with advanced NSCLC or metastatic NSCLC and PD-L1 TPS  $\geq$  50% without *EGFR* or *ALK* genomic alterations after 1L pembrolizumab monotherapy became reimbursed in the Czech Republic in February 2019.

## Patients and methods

### Data sources

This was a descriptive noninterventional study using the KELLY and TULUNG cancer registries in the Czech Republic [10–12]. Retrospective analysis of each registry database was conducted independently. No primary data collection, testing, or evaluations were performed in conjunction with the study.

Both TULUNG and KELLY registries are managed and rigorously monitored by the Institute of Biostatistics and Analyses (IBA), a spin-off company of Masaryk University that provides management, monitoring, and other services to the re-

gistries [13]. In this study, we used the KELLY registry to examine PD-L1 testing patterns from pathology records and the TULUNG registry to analyze targeted therapy utilization and pembrolizumab utilization with associated outcomes from medical records. Ethical review and approval were waived for this study because both the KELLY and TULUNG cancer registries are anonymized and operate independently without the option to merge data at the patient level.

Launched by IBA in 2014, the KELLY registry has been used as a source of anonymized data to monitor the number of Czech patients with NSCLC and their diagnostic testing [11,14]. Records include all newly diagnosed and microscopically verified NSCLC cases, histological parameters of each tumor, information about all morphological examinations, and *EGFR* and *ALK* testing performed in participating laboratories. Diagnostic data are entered in the registry once under a unique code. If a patient is re-examined, each sample is entered in the registry under a new unique code; therefore, the registry contains data at the sample level, not at the patient level. The registry is organized by type of material, i.e., small samples, small surgical specimens, and resection specimens. All small surgical and resection specimens can be tested for PD-L1 expression, whereas a small sample can be tested for PD-L1 expression only on cytoblock and biopsy.

The KELLY registry covers all laboratories authorized to perform PD-L1 immunohistochemistry (IHC) testing, as well as small laboratories that perform basic morphology and then send samples for further testing to the authorized laboratories. Since 2017, the registry has contained information on ~80% of all NSCLC samples in the Czech Republic. The PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA, USA), Anti-PD-L1 antibody [28-8] (abcam, Cambridge, UK), and VENTANA PD-L1 (SP263) Assay (Roche, Basel, Switzerland) are currently used as testing assays in the Czech Republic. The assays differ in the definition of PD-L1 positivity, which depends on the cells, tissue compartments, and staining thresholds for the specific PD-L1 assay.

The TULUNG registry is a noninterventional post-registration database collecting epidemiological and clinical data of patients with NSCLC who have been treated with selected therapies, primarily targeted therapies, including immunotherapy (e.g., alectinib, afatinib, atezolizumab, bevacizumab, ceritinib, crizotinib, dabrafenib, durvalumab, erlotinib, gefitinib, lorlatinib, nintedanib, nivolumab, osimertinib, pembrolizumab, pemetrexed, and trametinib). New therapies are added after their regulatory approvals, while platinum use (carboplatin or cisplatin) and generic drug use (e.g., docetaxel generic) are not recorded in TULUNG. The database covers all centers authorized to prescribe targeted therapies, including immunotherapies, in the Czech Republic. Clinicians enter the data voluntarily; however, they are reimbursed for their efforts. The TULUNG project was initiated in July 2011 by the Czech Society for Oncology, and data from the TULUNG registry can be enriched with mortality data from the national registry of death certificates.

### Patients

We identified patients with primary diagnostic samples or those who started 1L advanced or metastatic NSCLC treatment on or after February 1, 2019. Data were extracted from both registries on September 16, 2021. Since data are collected continuously in the TULUNG registry, the data collection period was from February 1, 2019, to September 16, 2021. In the KELLY registry, there is a lag of about 4 weeks between diagnostic testing (the reported date on the request form) and data input in the registry, so the data collection period was from February 1, 2019, to approx. August 19, 2021.

Three adult patient populations were included in this study to meet the three study aims, namely: (1) to describe PD-L1 testing patterns using the KELLY registry; (2) to describe therapy for advanced NSCLC as recorded in the TULUNG registry; and (3) to evaluate 1L pembrolizumab monotherapy utilization and outcomes for patients with metastatic NSCLC, using the TULUNG registry.

**Tab. 1. PD-L1 testing rates by year and quarter and sample turn-around time for 5,190 NSCLC samples submitted to the KELLY registry.**

Year and quarter	All NSCLC samples, N	Samples tested for PD-L1, N (%) <sup>a</sup>	Time from sample submission to release of PD-L1 results <sup>b</sup>			
			≤ 30 days, N (%)	31–60 days, N (%)	61–90 days, N (%)	> 90 days, N (%)
2019	2015	1420 (70.5)	1367 (96.3)	45 (3.2)	5 (0.4)	3 (0.2)
Q1	339	203 (59.9)	193 (95.1)	7 (3.4)	1 (0.5)	2 (1.0)
Q2	606	395 (65.2)	374 (94.7)	18 (4.6)	2 (0.5)	1 (0.3)
Q3	565	437 (77.3)	428 (97.9)	8 (1.8)	1 (0.2)	0
Q4	505	385 (76.2)	372 (96.6)	12 (3.1)	1 (0.3)	0
2020	2026	1645 (81.2)	1599 (97.2)	29 (1.8)	7 (0.4)	9 (0.5)
Q1	585	476 (81.4)	454 (95.4)	15 (3.2)	1 (0.2)	6 (1.3)
Q2	466	375 (80.5)	367 (97.9)	5 (1.3)	2 (0.5)	1 (0.3)
Q3	521	417 (80.0)	412 (98.8)	3 (0.7)	0	1 (0.2)
Q4	454	377 (83.0)	366 (97.1)	6 (1.6)	4 (1.1)	1 (0.3)
2021	1149	970 (84.4)	956 (98.6)	11 (1.1)	1 (0.1)	1 (0.1)
Q1	509	437 (85.9)	429 (98.2)	6 (1.4)	0	1 (0.2)
Q2	482	402 (83.4)	396 (98.5)	5 (1.2)	1 (0.2)	0
Q3	158	131 (82.9)	131 (100)	0	0	0

Sample dates were February 1, 2019, to approx. August 19, 2021.

<sup>a</sup> Percentages of samples tested for PD-L1 represent the percentage of all NSCLC samples during the time period.

<sup>b</sup> The time from the date of sample submission to the laboratory to the date of PD-L1 test result release, reported by a pathologist to the clinician. Percentages represent the percentage of total PD-L1 samples.

NSCLC – non-small cell lung cancer, PD-L1 – programmed death-ligand 1, Q – quarter (of each year)

#### PD-L1 testing patterns: KELLY registry

We included sample results from patients aged 18 years and older at the time of advanced NSCLC diagnosis, with histologically or cytologically confirmed diagnosis derived from the submitted sample and the primary diagnostic testing for NSCLC initiated on or after February 1, 2019, as recorded in the KELLY registry. Data from surgical resection specimens were excluded.

#### Therapy for advanced NSCLC: TULUNG registry

Patients eligible for descriptive analyses of targeted therapy including immunotherapy were ≥18 years old at the time of advanced NSCLC diagnosis, histologically or cytologically confirmed as at least stage IIIB NSCLC, and who initiated 1L therapy for advanced NSCLC on or after February 1, 2019.

#### First-line pembrolizumab monotherapy for metastatic NSCLC: TULUNG registry

Eligible patients were ≥18 years old at the time of a histologically or cytologically confirmed diagnosis of metastatic (stage IV) NSCLC, with PD-L1 TPS ≥ 50% and no known *EGFR* sensitizing mutation or *ALK* translocation (*EGFR/ALK* wild-type, or missing test results) confirmed before initiating 1L pembrolizumab monotherapy on/after February 1, 2019. Patients who received pembrolizumab for indications other than metastatic NSCLC were excluded, as were those who received 1L therapy in a clinical trial setting.

#### Outcomes and analyses

Using the KELLY registry, we calculated the percentages of tests for PD-L1 TPS among advanced NSCLC samples submitted each year and each quarter from February 1, 2019, to data cutoff (Sep-

tember 16, 2021). We also calculated the days from sample submission at the laboratory to availability of PD-L1 test results.

We described the characteristics of patients with advanced NSCLC in the TULUNG registry, in addition to the 1L targeted therapies administered to those with advanced NSCLC with PD-L1 TPS ≥ 50% during the study period. We also summarized characteristics of patients in the TULUNG registry who received 1L pembrolizumab monotherapy for metastatic NSCLC (PD-L1 TPS ≥ 50%, no known *EGFR/ALK* alteration) and analyzed two primary outcomes for this patient population. The real-world time on treatment (rwToT) was defined as the time from the first dose to the last dose of pembrolizumab (the earliest documented date among end-of-treatment dates, a recorded subsequent line of therapy, or date

of death while on therapy). If the date of the last dose was unavailable, the patient was censored on the date of the last structured activity (most recent visit, treatment date, or date of progression). OS was defined as the time from the first dose of pembrolizumab to death from any cause, with censoring on the date of the last structured activity.

We used descriptive statistics for continuous variables, namely, mean, standard deviation (SD), median, interquartile range (IQR), and range. Categorical variables were described using frequency and proportions. We calculated relative frequencies based on the number of patients/samples in the relevant subgroup. Time-to-event variables (OS, rwToT) were estimated using the Kaplan-Meier method. A minimum of 6 months of follow-up time from the start of 1L pembrolizumab and the cutoff date was required for the assessment of time-to-event variables.

## Results

### PD-L1 testing patterns:

#### KELLY registry

We identified 5,190 NSCLC samples submitted to the KELLY registry from February 1, 2019, to approx. August 19, 2021. The median age of patients with samples was 70 years (range, 20–99) and almost two-thirds were men (3,265; 63%); 3,000 samples (58%) were of non-squamous NSCLC histology (supplementary Tab. S1).

The percentage of NSCLC samples tested for PD-L1 increased over time from 71% in 2019 to 84% in 2021. Most PD-L1 results were released within 30 days (Tab. 1), and most samples were tested using the PD-L1 IHC 22C3 pharmDx assay, regardless of sampling year (supplementary Tab. S2). During the study period, 93% of samples (> 90% of samples during each quarter of each year) were associated with a primary diagnosis rather than a repeat examination (data not shown).

### Targeted therapy for advanced NSCLC: TULUNG registry

In the TULUNG registry, we identified 1,134 patients with advanced NSCLC who received targeted therapies inclu-

**Tab. 2. First-line targeted therapy including immunotherapy for 315 patients with advanced NSCLC with PD-L1 TPS  $\geq$  50% from February 1, 2019, to September 16, 2021, the TULUNG registry.**

1L targeted therapy, N (%)	Year of 1L initiation		
	2019 N = 92	2020 N = 134	2021 N = 89
afatinib	5 (5.4)	6 (4.5)	2 (2.2)
alectinib	4 (4.3)	4 (3.0)	5 (5.6)
bevacizumab	4 (4.3)	4 (3.0)	1 (1.1)
crizotinib	1 (1.1)	1 (0.7)	1 (1.1)
durvalumab	0	2 (1.5)	0
erlotinib	1 (1.1)	1 (0.7)	0
gefitinib	1 (1.1)	1 (0.7)	4 (4.5)
osimertinib	0	0	1 (1.1)
nivolumab	0	0	2 (2.2)
pembrolizumab	68 (73.9)	107 (79.9)	62 (69.7)
pemetrexed	8 (8.7)	8 (6.0)	2 (2.2)
pemetrexed + pembrolizumab	0	0	9 (10.1)

Specific targeted agents included in the TULUNG registry are alectinib, afatinib, atezolizumab, bevacizumab, ceritinib, crizotinib, dabrafenib, durvalumab, erlotinib, gefitinib, lorlatinib, nintedanib, nivolumab, osimertinib, pembrolizumab, pemetrexed, trametinib. No chemotherapy agents are reported.

1L – first line, PD-L1 – programmed death-ligand 1, NSCLC – non-small cell lung cancer, TPS – tumor proportion score

ding immunotherapy. Their median age was 68 years, over half (57%) were men, and the majority (81%) were current or former smokers. Other demographic and clinical characteristics of these patients are summarized in supplementary Tab. S3.

A total of 315 patients with advanced NSCLC and PD-L1 TPS  $\geq$  50% received 1L targeted therapy in 2019, 2020, and 2021. Most of these patients (70–80% each year) received 1L pembrolizumab monotherapy (Tab. 2). In 2021, 10% of patients received 1L pembrolizumab and pemetrexed.

### 1L pembrolizumab monotherapy for metastatic NSCLC: TULUNG registry

A total of 235 patients included in the TULUNG registry received 1L pembrolizumab monotherapy for stage IV NSCLC with PD-L1 TPS  $\geq$  50% and no known *EGFR* or *ALK* genomic alteration [15,16]. Their median age was 69 years (range

38–84); 126 (54%) patients were men; 232 (99%) were Caucasian; and 206 (88%) were current or former smokers (Tab. 3). All patients had Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 (reimbursement criteria), and 170 (72%) had nonsquamous NSCLC.

First-line pembrolizumab monotherapy was initiated with a median of 1 month after the NSCLC diagnosis (Tab. 3). The median follow-up period was 4.3 months (range 0–28) from the start of pembrolizumab to death or last structured activity before data cutoff.

The median number of pembrolizumab doses was 10 (range, 1–41; Tab. 4). The 213 patients (91%) with no recorded subsequent treatment included 125 patients (53%) who were still receiving pembrolizumab monotherapy at the end of the follow-up period and 88 patients (37%) who discontinued treatment. Twenty-two patients (9%)

**Tab. 3. Demographic and disease characteristics of patients with metastatic NSCLC, PD-L1  $\geq$  50%, no known *EGFR/ALK* genomic alteration, who received first-line pembrolizumab monotherapy, the TULUNG registry.**

N = 235	
Age, median (range), years	69.0 (37.9–84.1)
mean (SD)	68.3 (8.7)
Age, years, N (%)	
≤ 65 years	75 (31.9)
> 65 years	160 (68.1)
Sex, N (%)	
female	109 (46.4)
male	126 (53.6)
Race, N (%)	
Caucasian	232 (99.1)
other	2 (0.9)
missing	1
Smoking status, N (%)	
current	123 (52.3)
former	83 (35.3)
never	29 (12.3)
ECOG performance status, N (%) <sup>a</sup>	
0	47 (20.0)
1	188 (80.0)
NSCLC stage, N (%) <sup>a</sup>	
IV	42 (17.9)
IVA <sup>b</sup>	88 (37.4)
IVB <sup>b</sup>	105 (44.7)
NSCLC histologic type, N (%)	
squamous	65 (27.7)
nonsquamous	170 (72.3)
Time from diagnosis <sup>c</sup> to 1L therapy start, months	
mean (SD)	1.4 (1.9)
median (IQR), range	1.0 (0.7–1.6), 0.1–19.8

<sup>a</sup> American Joint Committee on Cancer (AJCC)-8 [15]; at the time of initiating pembrolizumab

<sup>b</sup> NSCLC stages IVA and IVB according to TNM, 8<sup>th</sup> edition [16]

<sup>c</sup> Date of diagnosis based on determination of tumor morphology (i.e., the date when the morphological diagnosis was established)

1L – first-line, ECOG – Eastern Cooperative Oncology Group, IQR – interquartile range, NSCLC – non-small cell lung cancer, PD-L1 – programmed death-ligand 1, SD – standard deviation

**Tab. 4. Details of first-line pembrolizumab monotherapy for 235 patients with metastatic NSCLC, the TULUNG registry.**

All patients N = 235	
Number of pembrolizumab cycles <sup>a</sup>	
mean (SD)	12.1 (10.1)
median (range)	10 (1–41)
Treatment duration, months <sup>b</sup>	
mean (SD)	8.8 (7.2)
median (range)	7.3 (0.0–28.4)
Treatment duration, N (%) <sup>b</sup>	
≥ 0 months	233 (100)
≥ 1 month	204 (87.6)
≥ 3 months	173 (74.2)
≥ 6 months	134 (57.5)
≥ 12 months	61 (26.2)
Pembrolizumab dosage <sup>c</sup>	
200 mg Q3W, N (%)	230 (97.9)
treatment duration, mean (SD), months <sup>b</sup>	8.6 (7.1)
treatment duration, median (range), months <sup>b</sup>	7.2 (0.0–28.4)
400 mg Q6W, N (%)	1 (0.7)
treatment duration, months	25.9
Other, N (%)	4 (1.7)
treatment duration, mean (SD), months	14.8 (7.2)
treatment duration, median (range), months	16.2 (4.9–22.0)
Subsequent therapy, N (%) <sup>d</sup>	22 (9.4)
pemetrexed	19 (86.4)
dabrafenib + trametinib	1 (4.5)
erlotinib	1 (4.5)
nivolumab	1 (4.5)

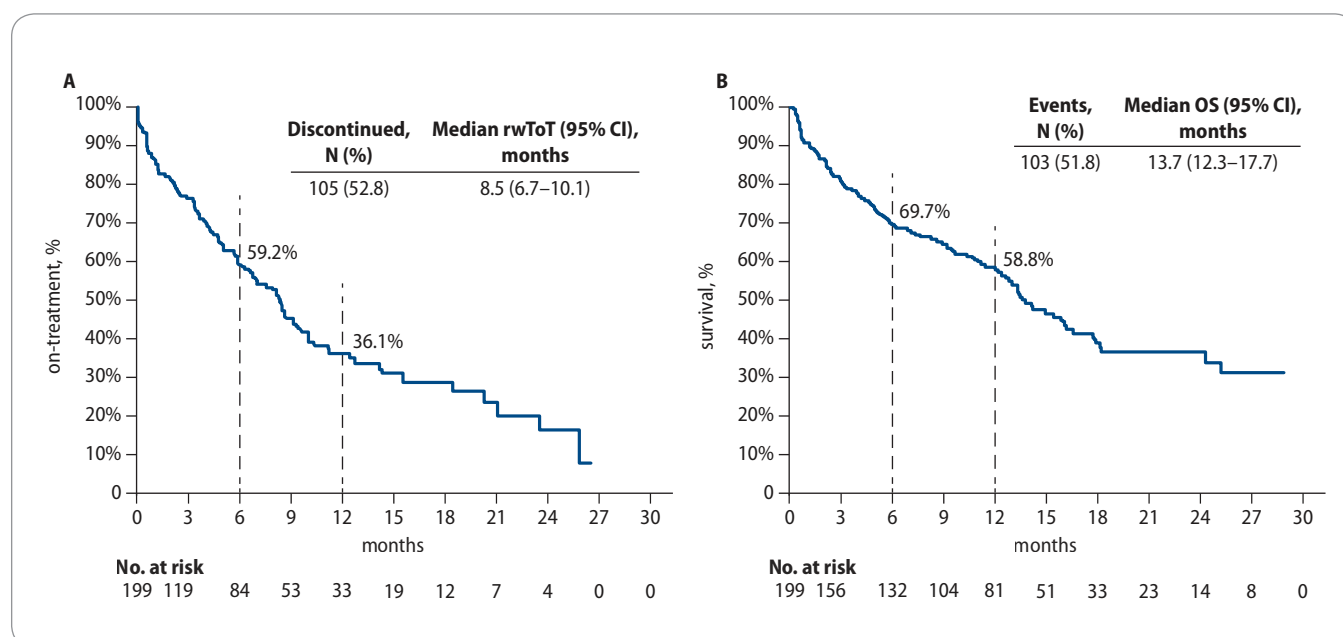
<sup>a</sup> Number of pembrolizumab cycles is reported for 229 patients, as the treatment end date for 2 patients was not recorded, and the dosage regimen for 4 patients was not entered.

<sup>b</sup> Treatment duration was missing for 2 patients who received 200 mg Q3W, as their treatment end date was not recorded.

<sup>c</sup> The dosage given during the entire treatment period. If the dosage changed, patients are categorized in the “other” dosage group.

<sup>d</sup> Any subsequent line of targeted treatment. No chemotherapy agents are reported.

Q3W – every 3 weeks, Q6W – every 6 weeks, NSCLC – non-small cell lung cancer, SD – standard deviation



**Fig. 1.** Kaplan-Meier plots of (A) real-world time on treatment and (B) overall survival (*post hoc* analysis) among patients with metastatic NSCLC treated with pembrolizumab monotherapy.

NSCLC – non-small cell lung cancer, OS – overall survival, rwToT – real-world time on treatment

treated with pembrolizumab monotherapy had subsequent therapy, most commonly pemetrexed, documented in the TULUNG registry (Tab. 4).

We evaluated OS and pembrolizumab rwToT for 199 patients (85%) with at least 6 months of follow-up. The median rwToT was 8.5 months, and the estimated on-treatment rates at 6 and 12 months were almost 60% and 36%, respectively (Fig. 1A). The median OS was not reached due to the low number of events (35, 18%).

We performed *post hoc* OS analyses in which we enriched data from the TULUNG registry with mortality data from the national registry of death certificates. (No changes other than adding dates of death were made in the dataset.) The minimum follow-up period was at least 6 months, and if a patient had a longer follow-up, their data were censored on the cutoff date (September 16, 2021). The median OS was 13.7 months (95% CI 12.3–17.7), and the estimated OS rates at 6 and 12 months were 70% and 59%, respectively (Fig. 1B).

## Discussion

Our study leveraged two population-based registries in the Czech Repub-

lic to describe real-world PD-L1 testing, treatment patterns, and clinical outcomes following access to 1L pembrolizumab monotherapy for metastatic NSCLC via public insurance reimbursement in 2019. Using data from the KELLY registry, we found that the percentage of advanced NSCLC samples tested for PD-L1 was high already at the study start and further increased during the study period. In 1Q 2019, shortly after pembrolizumab was made available to patients, the testing rate was nearly 60%. As PD-L1 testing was available in the Czech Republic (in January 2018) before access to pembrolizumab, hence, testing preceded therapy reimbursement by 13 months. This situation may explain why the testing percentages were high shortly after pembrolizumab became accessible. The percentage of advanced NSCLC samples tested for PD-L1 increased to nearly 83% in 3Q 2021 when this study ended.

Using data from the TULUNG registry, we found that among Czech patients with advanced NSCLC who received therapies of interest for the registry and had tumors with PD-L1 TPS  $\geq$  50%, about 70–80% were treated with 1L pembrolizumab monotherapy each year during

the study period. This percentage was the lowest in 2021 when 10% of patients received pembrolizumab with pemetrexed instead of monotherapy, a shift consistent with the reimbursement date for pembrolizumab with pemetrexed and platinum chemotherapy on March 1, 2021.

More than half of the 235 patients (58%) with metastatic NSCLC who received 1L pembrolizumab monotherapy were treated for more than 6 months and one-quarter (26%) were treated for 12 months or longer. The Kaplan-Meier median pembrolizumab rwToT was 8.5 months (95% CI 6.7–10.1), with estimated on-treatment rates at 6 and 12 months of almost 60% and 36%, respectively. This result is generally consistent with the median treatment duration for patients treated with 1L pembrolizumab monotherapy in clinical trials, namely, 7.9 months in KEYNOTE-024 [17,18], 6.6 months in patients with metastatic NSCLC and PD-L1 TPS  $\geq$  50% in the KEYNOTE-042 trial [19], and 9.7 months in the control group of patients with metastatic NSCLC and PD-L1 TPS  $\geq$  50% in the KEYNOTE-598 trial [20].

After supplementing mortality data from the TULUNG registry with records

from the national registry of death certificates, we estimated median OS of 13.7 months (95% CI 12.3–17.7). The estimated OS rate at 6 and 12 months was almost 70% and 59%, respectively. This 12-month rate was lower than in the KEYNOTE-024, KEYNOTE-042, and KEYNOTE-598 trials, with 12-month rates of 70.3%, 63.5%, and 67.9%, respectively [17,20,21]. These differences can be explained by prognostic patient characteristics in our real-world study compared with the clinical trial patient populations and/or differences in subsequent lines of therapy. Our patients were older, with median age of 69 years, while the median ages of patients in the trial pembrolizumab arms were 64.5 years in KEYNOTE-024, 63 years in KEYNOTE-042, and 65 years in KEYNOTE-598.

Our patient population also included more current smokers, 123 (52%), compared with 34 (22%) in KEYNOTE-024 and 76 (27%) in KEYNOTE-598 trials. In the pembrolizumab group with TPS  $\geq$  50% in the KEYNOTE-042 trial, 57 (19%) patients were current smokers [22], considerably fewer than in our study. A recent meta-analysis concluded that quitting smoking “at or around” the diagnosis improves survival in patients with lung cancer [23]. Squamous NSCLC histology was reported in 29 patients (19%) in KEYNOTE-024, while squamous histology percentage in our study was greater (65; 28%) and similar to 89 (33%) in KEYNOTE-042 and 77 (27%) in KEYNOTE-598.

Most patients in our study (188, 80%) had baseline ECOG PS of 1, while this performance status was reported in 99 (64%) in KEYNOTE-024, 187 (69%) in KEYNOTE-042, and 180 (63%) in KEYNOTE-598 [17,19,20]. In the KEYNOTE-024, KEYNOTE-042, and KEYNOTE-598 trial patient populations, life expectancy was required to be at least 3 months [5,20,22], whereas there was no such inclusion criterion in the real-world clinical setting.

As in any retrospective observational study, we cannot exclude an inherent bias mostly due to missing data. The data extracts were performed from live databases; thus, a data entry backlog or incomplete records might have occurred. It is not possible to iden-

tify patients included in both registries, so we could not associate records of the same patients. Reasons for not testing were unavailable for the samples that were not tested. We cannot exclude the possibility of misclassification, especially for ECOG PS. In the population treated with 1L pembrolizumab monotherapy, we found that all patients had ECOG PS of 0 or 1. Since ECOG PS is a subjective clinical measure and is tied to reimbursement in the Czech Republic, there is the possibility of misclassification if treated patients had a worse ECOG PS. The TULUNG registry includes only patients treated with targeted therapies; therefore, the information about subsequent treatment with chemotherapy was unavailable. As a result, we could not evaluate the time to next treatment (TTNT), which was an outcome of interest. Pembrolizumab in combination regimens approved by the EMA became only partially accessible during the study period; therefore, we were unable to evaluate outcomes for these regimens.

Our study adds to the paucity of literature on treatment patterns and real-world outcomes in patients with metastatic NSCLC treated in Central Europe after the EMA approval and pembrolizumab access roll-out [24]. A recent study compared the characteristics of patients in the German CRISP registry with metastatic NSCLC, PD-L1 TPS  $\geq$  50%, and treated with pembrolizumab monotherapy who would be potentially eligible with those who would not be eligible in the KEYNOTE-042 and -024 studies. The authors concluded that potentially eligible patients had better prognostic factors and better outcomes than potentially ineligible patients representing the real-world population [25]. In 2021, Frost et al. published results of a German retrospective multicentric study aiming to validate clinical trial results in real-world patients. They concluded that outcomes in frail patients with worse ECOG PS, brain metastases, and receiving corticosteroids were worse than in clinical trials [26]. The OS in both German studies was higher than in ours, likely because of different baseline characteristics of the studied populations; however, all three studies demonstrate

the effect of baseline characteristics on real-world patient outcomes.

## Conclusion

In real-world patients with metastatic NSCLC and PD-L1 TPS  $\geq$  50% treated with pembrolizumab monotherapy, the estimated OS rate at 12 months was 59%. This is lower than in the KEYNOTE-024, KEYNOTE-042, and KEYNOTE-598 trials, in which the 12-month rates were 70.3%, 63.5%, and 67.9%, respectively. Clinical trial patient populations are homogeneous per defined eligibility criteria, while real-world patient populations are heterogeneous. Differences in baseline patient characteristics in disease registries compared with randomized clinical trials should be considered when evaluating real-world clinical outcomes. Findings of this study highlight variations in patient characteristics in real-world settings compared with randomized clinical trials and their impact on clinical outcomes.

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## Potential conflicts of interest

Melissa L. Santorelli and Thomas Burke are full-time employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and hold stock of Merck & Co., Inc., Rahway, NJ, USA.

Goran Bencina was a full-time employee of Merck Sharp & Dohme LLC (MSD) at the time of the study and holds stock of Merck & Co., Inc., Rahway, NJ, USA.

Ondřej Fibigr has received speaker honoraria from GSK, AstraZeneca, MSD, Sanofi.

Leona Koubková has received support for attending meetings and speaker honoraria from Pfizer, Bristol Myers Squibb, MSD, AstraZeneca, Roche, Sanofi, Amgen, Merck and has served on advisory boards for Merck, MSD, Roche, Amgen.

Aleš Ryška has received consulting fees from Amgen, MSD, AstraZeneca, Boehringer-Ingelheim, Sanofi and speaker honoraria from Amgen, AstraZeneca, BMS, Eli Lilly, Janssen-Cilag, MSD, Roche, Gilead, Novartis, Sanofi, Merck Serono, Bayer; has served on advisory boards for Amgen, MSD, AstraZeneca, Sanofi; and has received support to his institution for attending meetings or travel from Sanofi, Gilead, Roche.

All other authors have declared no conflicts of interest. Employees of the funder participated in the design of the study; in the interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

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**For supplementary tables, see the online version of the article at [www.linkos.cz](http://www.linkos.cz).**

**Supplementary Tab. 1. Demographic and disease characteristics of patients with NSCLC tumor samples submitted to the KELLY registry.**

	NSCLC Samples
	N = 5,190
Age at time of tumor sample, years	
mean (SD)	69.1 (8.9)
median (range)	70 (20–99)
≤ 65 years, N (%)	1,483 (28.6)
> 65 years, N (%)	3,707 (71.4)
Sex, N (%)	
female	1,925 (37.1)
male	3,265 (62.9)
NSCLC histologic type, N (%)	
squamous	2,190 (42.2)
nonsquamous	3,000 (57.8)
NSCLC – non-small cell lung cancer	

**Supplementary Tab. 2. PD-L1 testing by year and type of assay, the KELLY registry.**

Year and quarter	All NSCLC samples, N	Tested for PD-L1, all and by assay antibody type, N (%)					Not tested for PD-L1, N (%)
		All	22C3	SP263	28-8	Another clone	
<b>2019</b>	2,015	1,420 (70.5)	1,322 (93.1)	35 (2.5)	11 (0.8)	52 (3.7)	595 (29.5)
Q1	339	203 (59.9)	194 (95.6)	0	1 (0.5)	8 (3.9)	136 (40.1)
Q2	606	395 (65.2)	363 (91.9)	7 (1.8)	8 (2.0)	17 (4.3)	211 (34.8)
Q3	565	437 (77.3)	396 (90.6)	24 (5.5)	2 (0.5)	15 (3.4)	128 (22.7)
Q4	505	385 (76.2)	369 (95.8)	4 (1.0)	0	12 (3.1)	120 (23.8)
<b>2020</b>	2,026	1,645 (81.2)	1,503 (91.4)	17 (1.0)	0	125 (7.6)	381 (18.8)
Q1	585	476 (81.4)	429 (90.1)	9 (1.9)	0	38 (8.0)	109 (18.6)
Q2	466	375 (80.5)	340 (90.7)	1 (0.3)	0	34 (9.1)	91 (19.5)
Q3	521	417 (80.0)	391 (93.8)	1 (0.2)	0	25 (6.0)	104 (20.0)
Q4	454	377 (83.0)	343 (91.0)	6 (1.6)	0	28 (7.4)	77 (17.0)
<b>2021</b>	1,149	970 (84.4)	901 (92.9)	62 (6.4)	1 (0.1)	6 (0.6)	179 (15.6)
Q1	509	437 (85.9)	386 (88.3)	45 (10.3)	1 (0.2)	5 (1.1)	72 (14.1)
Q2	482	402 (83.4)	385 (95.8)	16 (4.0)	0	1 (0.2)	80 (16.6)
Q3	158	131 (82.9)	130 (99.2)	1 (0.8)	0	0	27 (17.1)

Note: The percentages of samples tested (All) and not tested for PD-L1 represent the percentage of all NSCLC samples. The percentages for assay antibody type represent the percentages of all PD-L1 tests. NSCLC – non-small cell lung cancer, PD-L1 – programmed death-ligand 1

**Supplementary Tab. 3. Demographic and disease characteristics of 1,134 patients with advanced NSCLC who received targeted agents<sup>a</sup>, the TULUNG registry.**

	<b>N = 1134</b>
Age at first targeted treatment, years	
mean (SD)	66.8 (9.5)
median (range)	67.7 (24.2–90.1)
≤ 65 years, N (%)	423 (37.3)
> 65 years, N (%)	711 (62.7)
Sex, N (%)	
female	485 (42.8)
male	649 (57.2)
Race, N (%)	
Caucasian	1,116 (98.5)
other	17 (1.5)
missing	1
Smoking status, N (%)	
current	507 (44.7)
former	409 (36.1)
never	218 (19.2)
ECOG performance status, N (%) <sup>b</sup>	
0	211 (18.6)
1	887 (78.2)
2	36 (3.2)
NSCLC stage, N (%) <sup>b</sup>	
IIIB	76 (6.7)
IIIC (valid from TNM8)	39 (3.4)
IV	176 (15.5)
IVA (valid from TNM8)	369 (32.5)
IVB (valid from TNM8)	474 (41.8)
NSCLC histologic type, N (%)	
squamous	244 (21.5)
nonsquamous	890 (78.5)
Distant metastasis, N (%) <sup>b</sup>	N = 733
yes	556 (75.9)
no	177 (24.1)
PD-L1 expression status, N (%) <sup>c</sup>	N = 920
non-expressers	144 (15.7)
1–49% TPS	305 (33.2)
≥ 50% TPS	353 (38.4)
Undetermined	118 (12.8)
EGFR mutation, N (%) <sup>c</sup>	N = 839
mutant	151 (18.0)
wild-type	672 (80.1)
undetermined	16 (1.9)
ALK translocation status, N (%) <sup>c</sup>	N = 809

	<b>N = 1134</b>
positive	67 (8.3)
negative	716 (88.5)
undetermined	26 (3.2)
<i>ROS1</i> mutation status, N (%) <sup>c</sup>	N = 542
positive	12 (2.2)
negative	515 (95.0)
undetermined	15 (2.8)

<sup>a</sup> Specific targeted agents included alectinib, afatinib, atezolizumab, bevacizumab, ceritinib, crizotinib, dabrafenib, durvalumab, erlotinib, gefitinib, lorlatinib, nintedanib, nivolumab, osimertinib, pembrolizumab, pemetrexed, trametinib;

<sup>b</sup> AJCC version 8; at the time of initiating the first targeted treatment;

<sup>c</sup> biomarker testing before initiation of the first targeted treatment.

ECOG – Eastern Cooperative Oncology Group, NSCLC – non-small cell lung cancer, PD-L1 – programmed death-ligand 1