Acta Clin Croat 2025; 64:784-795
doi: 10.20471/acc.2025.64.04.16

Original Scientific Paper

REAL-WORLD CLINICAL OUTCOMES OF ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH HIGH PD-L1 EXPRESSION (≥50%) TREATED WITH PEMBROLIZUMAB MONOTHERAPY: EVIDENCE FROM A SINGLE UNIVERSITY HOSPITAL IN CENTRAL EUROPE

Jasmina Marić Brozić[1,2], Hrvoje Brčić[1], Klara Brčić[3], Kristina Urch[1], Neva Purgar Levarda[1], Jasna Radić[1,2] and Ana Fröbe[1,4]

[1]Department of Oncology and Nuclear Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia
[2]School of Medicine, University of Zagreb, Zagreb, Croatia
[3]Department of Hematology, Clinic for Internal Medicine, Sestre milosrdnice University Hospital Center, Zagreb, Croatia
[4]School of Dental Medicine, University of Zagreb, Zagreb, Croatia

SUMMARY − Pembrolizumab, a programmed death-1 (PD-1) immune checkpoint inhibitor, has demonstrated significant survival benefits as monotherapy in clinical trials for advanced non-small cell lung cancer (NSCLC) with high programmed death ligand-1 (PD-L1) expression (PD-L1 ≥50%). Real-world data on this topic is growing every day.

We conducted a single-center, retrospective observational study at Sestre milosrdnice University Hospital Center in Zagreb, Croatia, analyzing the outcomes of patients with advanced NSCLC (stage IIIB–IV) and high PD-L1 expression treated with pembrolizumab as first-line monotherapy between March 2018 and March 2023. Demographic and clinical data including treatment response, adverse events, progression-free survival (PFS) and overall survival (OS) were analyzed using descriptive statistics and the Kaplan-Meier survival analysis, with multivariate Cox regression for covariate assessment.

Seventy-two patients met the inclusion criteria. Median follow-up was 49 months. Median PFS and OS were 13 months (95% CI: 5–20 months) and 24 months (95% CI: 14–46 months), respectively. One-year OS rate was 66.67%. Pembrolizumab demonstrated a favorable safety profile, with adverse events consistent with those reported in clinical trials.

This study highlights the real-world effectiveness and safety of pembrolizumab monotherapy for advanced NSCLC with high PD-L1 expression in a single-center cohort. Survival outcomes were consistent with clinical trial data.

Keywords: *Pembrolizumab; NSCLC; PD-1; PD-L1; Immunotherapy*

Correspondence to: *Hrvoje Brčić*
Department of Oncology and Nuclear Medicine,
Sestre milosrdnice University Hospital Center,
Vinogradska cesta 29, Zagreb, Croatia
e-mail: hrvoje.brcic@kbcsm.hr

Received March 1, 2025, accepted May 26, 2025

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for nearly one in five cancer-related fatalities. In 2022, there were approximately 2.5 million new lung cancer diagnoses globally, representing 12.4% of all cancers, making it the most commonly diagnosed cancer worldwide[1]. Non-small cell lung cancer (NSCLC) is the most prevalent, comprising approximately 85% of all lung cancer diagnoses[2]. Oftentimes patients with NSCLC present at an advanced stage of disease: unresectable or metastatic (Stage IIIB/C-IV)[3].

Historically, the median overall survival (mOS) for patients with metastatic NSCLC receiving only supportive care was roughly 4 to 5 months. However, the survival rate can improve to 8–12 months when chemotherapy is administered[4]. Over the past decade, the treatment of advanced-stage NSCLC has made substantial progress, primarily due to the discovery and development of targeted therapies and immunotherapies. The identification of actionable oncogenic driver mutations, such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangements, has revolutionized treatment strategies for a select group of NSCLC patients. The abovementioned targeted therapies have significantly improved survival outcomes for NSCLC patients with these genetic alterations[5,6].

However, a significant proportion of NSCLC patients does not harbor these oncogenic mutations[7]. For this group of NSCLC patients, immunotherapy has emerged as a major breakthrough. Immune checkpoint inhibitors (ICIs) target specific immune receptors, such as Programmed Death-1 (PD-1), which is a key regulator of immune response and self-tolerance. PD-1 is involved in suppressing immune responses by regulating the activity of T-cells within the tumor microenvironment. By blocking the interaction between PD-1 on T-cells and Programmed Death Ligand-1 (PD-L1) on tumor cells, ICIs boost the body's immune system, enabling it to better recognize and attack cancer cells[8]. Pembrolizumab, a humanized IgG4 monoclonal antibody, disrupts the PD-1/PD-L1 interaction and has become a cornerstone in the treatment of advanced NSCLC[9].

The role of pembrolizumab in the treatment of advanced NSCLC has been well established through several clinical trials, including KEYNOTE-001[10], KEYNOTE-010[11], KEYNOTE-042[12] and KEYNOTE-024[13]. The KEYNOTE-024 trial, in particular, demonstrated the efficacy of pembrolizumab as a first-line monotherapy for patients with metastatic NSCLC and high PD-L1 expression (tumor proportion score (TPS) ≥ 50%). This trial showed a remarkable improvement in 5-year overall survival rates — 31.9% in the pembrolizumab group compared to 16.3% in the chemotherapy group[13]. Additionally, the KEYNOTE-189[14] and KEYNOTE-407[15] trials have confirmed the benefit of combining pembrolizumab with chemotherapy, both in non-squamous and squamous NSCLC subtypes. Pembrolizumab combined with pemetrexed and platinum became available for non-squamous NSCLC patients with TPS PD-L1 < 50% based on the KEYNOTE 189 trial, which showed significantly better OS (12-month overall survival rate 71.5% vs. 50.9%; 5-year OS rate 19.4% vs 11.3%, HR: 0.60, 95% CI 0.50–0.72) and PFS compared to chemotherapy alone[14]. Also, outcomes from a 5-year follow-up from KEYNOTE-407 were reported showing that pembrolizumab with chemotherapy improved OS and PFS compared to placebo with chemotherapy in the first-line treatment of metastatic squamous NSCLC (with 5-year OS rates of 18.4% vs 9.7%)[15]. Therefore, pembrolizumab has demonstrated sustained efficacy in OS, both as monotherapy and in combination with chemotherapy in selected patients under controlled clinical trials.

Despite these promising results in clinical trials, it is still crucial to assess the real-world effectiveness of pembrolizumab in treating advanced NSCLC, particularly in settings outside the controlled environment of randomized clinical trials. Trials often face challenges when testing diverse patient subgroups, especially considering the heterogeneous nature of cancer biology, which calls for more personalized approaches to treatment. Additionally, participants in clinical trials adhere to strict drug administration protocols and undergo regular radiographic follow-ups. However, in real-world settings, patient care varies across clinics and such strict protocols may not always be followed, raising the question of whether clinical trial results can be replicated in everyday medical practice. Real-world data can provide valuable insights into the actual effectiveness of pembrolizumab in clinical practice,

shedding light on factors such as patient heterogeneity, the impact of comorbidities and variations in treatment protocols that are not fully captured in clinical trials[16].

The majority of the available real-world data on immunotherapy outcomes for NSCLC comes from North America and Western Europe, with a significant portion involving pre-treated patients and patients who were treated with other immune checkpoint inhibitors, or with a combination of ICI and chemotherapy[17].

In a recent study in Central Europe, a 1-year OS of 62% was reported in patients treated with immunotherapy as first-line treatment (as monotherapy or in combination with chemotherapy), but the report was not limited to pembrolizumab monotherapy[18].

This study aimed to provide evidence from a single academic center in Croatia, focusing on the use of first-line pembrolizumab monotherapy for treating advanced NSCLC in treatment-naïve patients with a high PD-L1 expression (PD-L1 ≥ 50%). By evaluating the clinical outcomes, safety profile and patient characteristics in a real-world setting, we aimed to contribute valuable insights that complement the findings from clinical trials and offer a more comprehensive understanding of the effectiveness of pembrolizumab in routine clinical practice.

Methods

Study Design and Patients

This study was a single-center, retrospective, observational analysis conducted in Zagreb, Croatia at Sestre milosrdnice University Hospital Center, specifically within its Department of Oncology and Nuclear Medicine. The primary aim was to evaluate the real-world outcomes of patients with advanced NSCLC who had high PD-L1 expression (≥ 50%) and were treated with anti PD-1 therapy (pembrolizumab) as first-line monotherapy for treatment-naïve patients.

The study included consecutive adult patients (> 18 years) who had been diagnosed with a locally advanced stage IIIB/C (non-resectable) or metastatic (stage IV) NSCLC, confirmed with pathological findings. Patients were included in the study starting from March 2018, through to March 2023, with the data cut-off set at December 2024.

Patients with a history of hepatitis B or C, or HIV infection, and those with a severe autoimmune disease were not included. Patients who harbored known actionable driver mutations were also excluded. To assess this, all patients underwent testing for the most common oncogenic mutations, including EGFR mutations, ALK rearrangements and reactive oxygen species proto-oncogene 1 (ROS1) alterations. While Kirsten Rat Sarcoma viral oncogene homolog (KRAS) testing is often performed globally due to the availability of targeted treatments for this mutation, these therapeutic options are currently unavailable in Croatia, which explains why KRAS testing was not performed routinely for the patients in this cohort.

PD-L1 Expression Assessment

All patients in the study were evaluated for tumor PD-L1 expression levels using the VENTANA PD-L1 (SP263) Assay, a widely used diagnostic test. To meet the inclusion criteria for this study, tumor tissue had to exhibit a PD-L1 TPS of ≥ 50%.

Treatment Protocol

The treatment protocol followed the standard clinical practice for pembrolizumab administered as a first-line monotherapy. Pembrolizumab was administered following two different dosing schedules: 200 mg intravenously every 3 weeks or 400 mg intravenously every 6 weeks.

Data Collection

Data for this study were obtained from the hospital registry at Sestre milosrdnice University Hospital Center. Given the retrospective nature of the study, patient consent was not required, as the research involved only the analysis of existing anonymized data. All patient information was collected in compliance with relevant ethical standards, ensuring confidentiality and the protection of personal identifiers.

The data collected from the registry included a variety of patient-specific and clinical characteristics. Demographic information such as age, sex and smoking history were recorded, as well as the specific characteristics of each patient's NSCLC, including histology, disease stage, and prior and later treatments. Tumor response to therapy and toxicity profiles associated with pembrolizumab treatment were also documented.

Study Measures and Statistical Analysis

The outcome was assessed using imaging methods (usually CT scan or PET-CT scan). In line with routine clinical practice, patients who showed a good initial response (complete response (CR), partial response (PR) or stable disease (SD)) continued treatment and were assessed radiologically every three months. Their response was analyzed according to the Immunotherapy Response Evaluation Criteria in Solid Tumors (iRECIST)[19]. For patients who died during treatment, the clinical progression category was applied.

To estimate survival outcomes, PFS and OS were calculated using the Kaplan-Meier method. Median follow-up was calculated with the reverse Kaplan-Meier. OS was calculated from the start of treatment until death from any cause. PFS was calculated from the

Table 1. Baseline patient characteristics

Baseline characteristics					
	N	**Minimum**	**Maximum**	**Median**	**IQR**
Age at start of treatment, years	72	31	83	66.22	13
Age at start of treatment, years (female)	25	45	79	64	9
Age at start of treatment, years (male)	47	31	83	68	15
		Frequency (N)		Percent (%)	
Sex	Female	25		34.72	
	Male	47		65.28	
Smoking status	Current	50		69.44	
	Non-current	22		30.56	
Histology	Adenocarcinoma	44		61.11	
	Carcinoma planocellulare	18		25.00	
	NSCLC-NOS	7		9.72	
	Pleomorphic carcinoma, large cell	1		1.39	
	Sarcomatoid carcinoma	1		1.39	
	Large cell carcinoma	1		1.39	
Disease stage	Metastatic (De novo)	63		87.50	
	Unresectable	3		4.17	
	Unresectable recurrence	2		2.78	
	Metastatic recurrence	4		5.56	
ECOG PS	0	41		56.94	
	1	26		36.11	
	2	5		6.94	
PD-L1	> 90%	20		27.78	
	50-89%	52		72.22	
Brain metastasis	Yes	16		22.22	
	No	56		77.78	

IQR = interquartile range; NSCLC-NOS = Non-small cell lung carcinoma, not otherwise specified; NSCLC = Non-small cell lung cancer; ECOG = Eastern Cooperative Oncology Group; PS = performance status; PD-L1 = Programmed Cell Death Ligand 1; ALK = Anaplastic Lymphoma kinase; ROS = Rearrangement of c-ros oncogene 1; EGFR = Epidermal growth factor receptor.

start of treatment until disease progression or death. According to predefined study criteria, even death in the absence of radiological signs of disease progression was counted as an event. For further analysis, a multivariate Cox regression hazard model was applied to assess the impact of various covariates on survival outcomes. *P*-values of < 0.05 were considered statistically significant. Adverse events were recorded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5[20]. All statistical analyses were performed using the SAS (Statistical Analysis Software) program.

Results

Baseline Characteristics

The study included 72 patients. Among these patients, the majority were male, accounting for approximately two-thirds of the cohort (N = 47, 65.28%), while 25 patients were female (34.72%). The median age of the patients was 66.22 years, range 31–83, IQR 13.

At the time of data analysis, 50 patients (69.44%) identified themselves as current smokers. A third of the patients (N = 22, 30.56%) identified themselves as either former or never smokers.

The majority of patients had adenocarcinoma (N = 44, 61.11%). A smaller subset of patients had squamous cell carcinoma (N = 18, 25.00%), while the minority of cases (N = 10, 13.89%) were categorized as not otherwise specified (NSCLC-NOS), pleomorphic carcinoma, sarcomatoid carcinoma and large cell NSCLC.

Regarding disease stage, 63 patients (87.50%) had *de-novo* metastatic NSCLC. A smaller percentage of patients presented with unresectable disease (N = 3, 4.17%), while 2 patients (2.78%) had a locally advanced unresectable recurrence and 4 patients (5.56%) had a metastatic recurrence.

Most of the patients were Eastern Cooperative Oncology Group (ECOG) Performance Status 0 (N = 41, 56.94%) or ECOG 1 (N = 26, 36.11%). Few cases had ECOG > 1 (N = 5, 6.95%).

A total of 20 (27.78%) patients had PD-L1 scores above 90%. A total of 16 (22.22%) patients had brain metastases. Patient baseline characteristics are shown in Table 1.

Effectiveness

Regression (partial and complete) accounted for the largest proportion of best outcomes during treatment. Partial regression was the most frequent individual outcome, representing 35 (48.61%) of all cases. Effectiveness is shown in Table 2.

Table 2. Best outcome during treatment

Best outcome		**Frequency (N)**	**Percentage (%)**
Regression	Total	39	54.17
	Complete	4	5.56
	Partial	35	48.61
Stable disease	Total	4	5.56
Progression	Total	29	40.27
	Radiological	15	20.83
	Clinical	14	19.44

Treatment Characteristics

Seventeen patients (23.61%) finished 2 years of immunotherapy with pembrolizumab. The median number of therapy cycles was 6 (SD 12.08) for all patients. Outliers had longer treatment duration — up to 48 cycles. A smaller subset of patients (N = 19, 26.39%) progressed and received second-line therapy after failure of first-line therapy. Treatment characteristics are shown in Table 3.

Survival Analysis

Median follow-up was 49 months (95% CI 40–55 months). The Kaplan-Meier survival analysis included all (N = 72) patients, of which 43 (59.72%) experienced events (death), while 29 were censored, resulting in a censoring rate of 40.28%. The median survival time (mOS) for the entire cohort was 24 months with a 95% CI of 14–46 months (Figure 1). Survival probabilities declined over time, with 75% surviving after 6 months and 66.67% surviving at 12 months. The survival rate at 49 months (median follow-up) dropped to 38%. The survival curve showed a sharp decrease during the initial two years, indicating a critical period

Table 3. Treatment characteristics

Treatment characteristics			
		Median	**SD**
Number of cycles in 1st line		6	12.08
		Frequency (N)	Percent (%)
Completed 2 years of treatment	Yes	17	23.61
	No	55	76.39
Second-line treatment	Yes	19	26.39
	No	53	73.61
Adverse Events	Yes	31	43.06
	No	41	56.94
Treatment-related death (susp.)		2	2.74
Adverse Events category	Pneumonitis	9	27.27
	Transaminase elevation	7	21.21
	Thyroiditis	4	12.12
	Rash	3	9.09
	Diabetes mellitus	2	6.06
	Other	8	24.25
CTCAE	Grade 1	8	25.81
	Grade 2	11	35.48
	Grade 3	9	29.03
	Grade 4	1	3.23
	Grade 5	2	6.45
Adverse events leading to therapy discontinuation		19	61.29
Adverse events leading to hospitalization		5	16.13

CTCAE = Common Terminology Criteria for Adverse Events

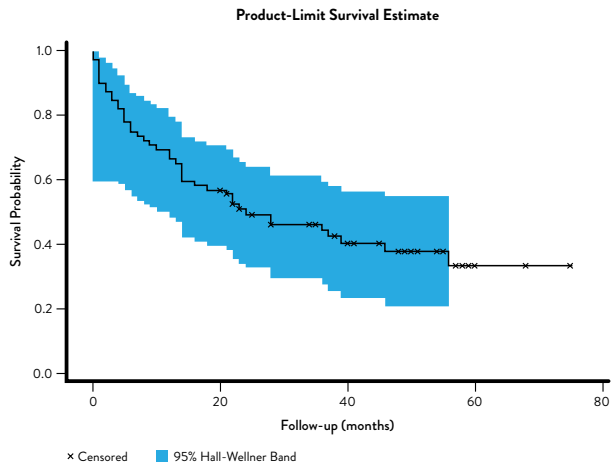

Figure 1. Kaplan-Meier estimates of overall survival

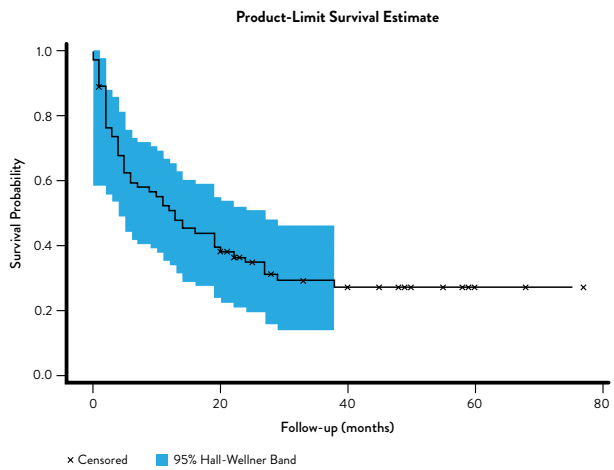

Figure 2. Kaplan-Meier estimates of progression-free survival

for patient outcomes. After 36 months, the survival probability plateaued.

Median progression-free survival (mPFS) was estimated at 13 months with a 95% CI of 5–20 months (Figure 2). At 11 months, the probability of progression-free survival was 52.2%, declining to 38.1% at 20 months. Fifty patients (69.4%) progressed or failed, while 22 (30.6%) were censored. The 25th percentile was reached at 3 months (95%: CI 2–5 months) and the 75th percentile at 24 months, though the upper confidence limit could not be estimated.

Adverse events

Adverse events were commonly reported. The distribution of adverse event grade according to CTCAE v 5.0 are summarized in Table 3. Thirty-one events were recorded (43.06%). Grade 2 adverse events were the most frequent, accounting for 33.33% of all

reported events. Serious adverse events (grade 4 and 5) were relatively rare, with grade 4 accounting for 3.33% of all reported events. Pneumonitis was the most frequently reported adverse event, mostly leading to treatment discontinuation. The second most common adverse event was transaminase elevation (Figure 3).

Of all the adverse events, five (16.13%) events lead to hospitalization, with transaminase elevation (23.33%) and pneumonitis (20.0%) being the most common reasons. Grade 5 adverse events were reported for two patients (6.45%); one patient experienced liver transaminase elevation and respiratory failure following the second cycle of therapy, and the other patient developed worsening paraneoplastic syndrome (PNS) after the first cycle of pembrolizumab. No autopsy was performed on either patient, so the exact cause of death remains undetermined.

Multivariate analysis

A Cox regression hazard model was performed to identify predictors of overall survival in our cohort of patients. The model was adjusted for multiple variables including age at start of treatment, sex, smoking status, ECOG performance status, histology, the presence of brain metastases, PD-L1 expression (50–89%/> 90%), the completion of 2 years of pembrolizumab, second-line treatment (after progression on pembrolizumab) and the presence of adverse events. The model as a whole was statistically significant, indicating that the predictors collectively affected overall survival in this cohort ($P < 0.0001$).

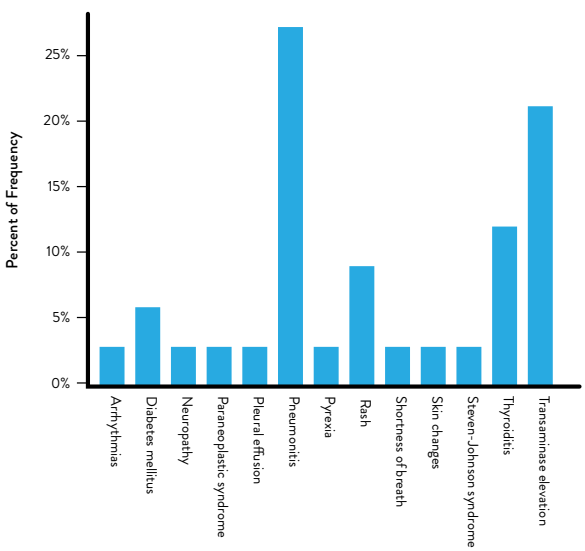

Figure 3. Percentage of the frequency of adverse events

In the analysis of variables, sex, ECOG score, second-line treatment and the completion of two years of therapy were identified as significant predictors of overall survival. Of these, the most impactful factor was completing two years of immunotherapy; patients who did not complete 2 years of treatment had a higher risk of death (HR: 15.632, $P = 0.0005$).

Patients who received second-line treatment had a 59.2% lower risk of death (HR: 0.408, $P = 0.0307$).

Better performance status (ECOG 0-1) was associated with a 66.9% reduced risk of death compared to ECOG 2 patients (HR: 0.331, $P = 0.0354$).

Female patients had a 58.7% reduced risk of death compared to males (HR: 0.413, $P = 0.0288$).

The Cox regression hazard model was done to identify predictors of PFS. The model was adjusted for multiple variables, including age at start of treatment, sex, smoking status, ECOG performance status, histology, presence of brain metastasis, PD-L1 expression (50–89%/> 90%) and the presence of adverse events.

Adverse events had a protective effect on progression, with patients experiencing adverse events showing a 67.2% lower risk of progression (HR: 0.328, $P = 0.0014$).

Other variables showed trends, but were not statistically significant.

Discussion

This study provides insights into the clinical application of pembrolizumab in NSCLC patients with high PD-L1 expression, revealing important trends in treatment response, survival outcomes and adverse event profiles.

The limitations of this study, including its retrospective design and relatively small sample size, must be acknowledged when interpreting the findings. It should be noted that the wide confidence intervals around median survival time reflect the influence of censoring and the limited number of patients remaining at risk during later follow-up periods. On the other hand, our study had a longer median follow-up time

than most of the published real-world data on pembrolizumab monotherapy in high PD-L1 expression advanced NSCLC patients to date[21–27].

A real-world retrospective study by Hektoen et al.[27], had a noteworthy similar median follow-up in their mono-pembrolizumab cohort of 48 months, but with significantly more patients (N = 1179). In this Norwegian study, mOS was significantly lower than in our study results (13.8 vs 24 months), but there was a big proportion of patients who had PD-L1 < 50% (17% vs 0%), and there was a significant difference in ECOG PS > 1 patients (27% vs 6.94%).

We found only one retrospective observational real-world study performed in the United States that had a longer median follow-up time than our study. We only took into account studies on advanced NSCLC that observed patients with high PD-L1 expression and pembrolizumab monotherapy. The median follow-up in this US study was 60.5 months. Looking at the study protocol, we found that this retrospective study only included patients with ECOG PS 0–1. Median OS in this study was 19.2 months, which is slightly lower than in our study, but there was a significant proportion of patients older than 75 years (39%) and the median age of the patients was significantly higher than in our study (72 vs 66 years)[28].

Although pembrolizumab therapy demonstrated efficacy in a substantial proportion of patients, the high rate of progression (almost half of the patients (40.27%) had progression as the best overall response in our study) underscores the reality that not all patients respond favorably to pembrolizumab monotherapy, even with high PD-L1 expression.

Our results suggest that completing the two-year treatment is crucial for patient outcomes. This is in line with KEYNOTE-010 findings, where the 5-year OS rates for pembrolizumab vs docetaxel were 25.0% vs 8.2% in patients with PD-L1 TPS ≥ 50%, but among 79 patients who completed 35 cycles/2 years of pembrolizumab, the OS rate 3 years after completion (approximately 5 years from randomization) was 83.0%[11]. In our study, the survival curve showed a sharp decrease during the initial two years. After 36 months, the survival probability plateaued. The fact that a portion of patients survived well beyond the mOS of 24 months emphasizes the potential for long-term benefits in some individuals, possibly highlighting a subgroup with distinct biological or immune characteristics other than PD-L1 expression. This suggests that additional biomarkers, beyond PD-L1 expression, may be required to predict response more accurately. This hypothesis of multiple potential biomarkers of clinical relevance is already established across different types of tumors, for example prostate cancer[29]. Next-generation sequencing (NGS) could be the key to finding these additional biomarkers, but unfortunately it is still not part of everyday clinical practice for all patients with NSCLC[30].

Other tumor biomarkers alongside high PD-L1 expression could suggest why some of the patients still benefit from additional chemotherapy and do not respond well to pembrolizumab monotherapy[31,32].

Additionally, nearly a quarter of the patients in our data had brain metastases at the time of diagnosis, which highlights an important clinical challenge in managing advanced NSCLC in real-world clinical practice. The incidence of brain metastases in KEYNOTE-024 was only 11.7% in the pembrolizumab arm[12]. In our real-world data, 22.22% patients had brain metastases. This also aligns with the incidence in other real-world data which, according to a systematic review by Macioch et al., states that the median incidence of brain metastases in real-world data is around 19.3%[33].

The Cox regression analysis in our study revealed that sex, second-line therapy, ECOG performance status and treatment duration were significant predictors of OS. The association of better performance status (ECOG 0-1) with improved OS further supports the notion that patients with better functional status may tolerate and benefit from extended immunotherapy, which is consistent with other real-world data results[21–24,33]. Female patients tend to have better outcomes than male patients (although this was not statistically significant in our study, HR: 0.413, $P = 0.0288$), which is also observed in other real-world data published so far. According to a systematic review by Macioch et al. looking at all available data on pembrolizumab monotherapy for a NSCLC patient, there is a tendency for female patients to have better outcomes than male patients[33].

Moreover, the inverse relationship between the completion of 2 years of pembrolizumab therapy and the risk of death suggests that a longer duration

of treatment provides substantial survival benefits. Stopping the treatment after 2 years is in accordance with other clinical practices around the world[34]. It is noteworthy that some patients, classified as outliers, received treatment with significantly longer durations. Looking at the median time of treatment and the number of cycles received, the median number of cycles in our study was 6 (the median number of cycles in the pembrolizumab arm in KEYNOTE-024 published in 2016 was 10.5), which further suggests that a lot of patients progressed on the upfront pembrolizumab monotherapy even though they had high PD-L1 expression. In our study, almost a quarter of the patients (N = 17, 23.61%) completed 2 years of immunotherapy, meaning that the number of cycles that was given to them was substantially higher than the median number of cycles given to all high PD-L1 expression NSCLC patients. One-quarter (25.32%) of the patients received 2 years of immunotherapy in the KEYNOTE-024 study as well. Furthermore, in our analysis, very-high PD-L1 expression (TPS > 90%) was not a statistically significant predictor of PFS or OS, even though there is a lot of published data suggesting that these patients benefit more from pembrolizumab monotherapy; we have seen a trend toward this in our analysis, but without true statistical significance. We must acknowledge that for the data on very-high PD-L1 expression patients, the reason for the absence of positive predictability could be a lower number of studied patients with very high PD-L1 expression (N = 20, 27.78%) than the one present in other real-world studies[35–37].

The fact that second-line treatment, which in our analysis was mainly chemotherapy, statistically seems to improve patient outcomes further deepens the question if some of the patients with high PD-L1 expression would still benefit more from upfront combination therapy rather than just ICI monotherapy.

Patients who experienced immune-related adverse events had a significantly lower risk of progression. This could be indicative of a potential link between immune system activation and delayed progression, but it is crucial to recognize that these events can have detrimental effects on quality of life and overall patient well-being. These adverse events are indicative of a more robust immune response and therefore correlate with better treatment outcomes[38,39], but we must admit that the observed risks of serious adverse events, including death, complicate interpretation. The occurrence of grade 5 adverse events, resulting in fatalities in two patients (although not confirmed by autopsy, but with high clinical suspicion) underscores the need for careful patient monitoring and individualized management, particularly in those with underlying conditions, such as paraneoplastic syndromes[40].

In conclusion, pembrolizumab is an effective monotherapy treatment strategy in most of the high PD-L1 positive patients and our results are in accordance with other real-world data findings and with the KEYNOTE-024 clinical trial. Further prospective, large cohort studies with other predictive and prognostic biomarkers are needed to discern the optimal treatment choice to achieve better treatment outcomes for all high PD-L1 expressing patients with advanced NSCLC.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024 May-Jun;74(3):229-263. doi: 10.3322/caac.21834. Epub 2024 Apr 4.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024 Jan-Feb;74(1):12-49. doi: 10.3322/caac.21820. Epub 2024 Jan 17. Erratum in: CA Cancer J Clin. 2024 Mar-Apr;74(2):203. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al.Petrella F, Spaggiari L, Rosell R. Non-small-cell lung cancer. Nat Rev Dis Primers. 2015 May 21;1:15009. doi: 10.1038/nrdp.2015.9.
3. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Suppl 4):iv192-iv237. Casal-Mouriño A, Ruano-Ravina A, Lorenzo-González M, Rodríguez-Martínez Á, Giraldo-Osorio A, Varela-Lema L, Pereiro-Brea T, Barros-Dios JM, Valdés-Cuadrado L, Pérez-Ríos M. Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. Transl Lung Cancer Res. 2021 Jan;10(1):506-518. doi: 10.21037/tlcr.2020.03.40.
4. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK et al. Chemotherapy can prolong survival in patients

with advanced non-small-cell lung cancer--report of a Canadian multicenter randomized trial. J Clin Oncol. 1988 Apr;6(4):633-41. doi: 10.1200/JCO.1988.6.4.633.

5. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH et al.; FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125. doi: 10.1056/NEJMoa1713137. Epub 2017 Nov 18.
6. Arbour KC, Riely GJ. Diagnosis and Treatment of Anaplastic Lymphoma Kinase-Positive Non-Small Cell Lung Cancer. Hematol Oncol Clin North Am. 2017 Feb;31(1):101-111. doi: 10.1016/j.hoc.2016.08.012.
7. Friedlaender A, Perol M, Banna GL, Parikh K, Addeo A. Oncogenic alterations in advanced NSCLC: a molecular super-highway. Biomark Res 12, 24 (2024). doi: 10.1186/s40364-024-00566-0.
8. Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. Am J Cancer Res. 2020 Mar 1;10(3):727-742.
9. Kwok G, Yau TC, Chiu JW, Tse E, Kwong YL. Pembrolizumab (Keytruda). Hum Vaccin Immunother. 2016 Nov;12(11):2777-2789. doi: 10.1080/21645515.2016.1199310. Epub 2016 Jul 11.
10 Garon EB, Hellmann MD, Rizvi NA, Carcereny E, Leighl NB, Ahn MJ et al. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. J Clin Oncol. 2019 Oct 1;37(28):2518-2527. doi: 10.1200/JCO.19.00934. Epub 2019 Jun 2.
11. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol. 2021 Oct;16(10):1718-1732. doi: 10.1016/j.jtho.2021.05.001. Epub 2021 May 26.
12. Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ et al; KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019 May 4;393(10183):1819-1830. doi: 10.1016/S0140-6736(18)32409-7. Epub 2019 Apr 4.
13. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. J Clin Oncol. 2019 Mar 1;37(7):537-546. doi: 10.1200/JCO.18.00149. Epub 2019 Jan 8.
14. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023 Apr 10;41(11):1992-1998. doi: 10.1200/JCO.22.01989. Epub 2023 Feb 21.
15. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol. 2023 Apr 10;41(11):1999-2006. doi: 10.1200/JCO.22.01990.
16. Verkerk K, Voest EE. Generating and using real-world data: A worthwhile uphill battle. Cell. 2024 Mar 28;187(7):1636-1650. doi: 10.1016/j.cell.2024.02.012.
17. Juarez-Garcia A, Sharma R, Hunger M, Kayaniyil S, Penrod JR, Chouaïd C. Real-world effectiveness of immunotherapies in pre-treated, advanced non-small cell lung cancer Patients: A systematic literature review. Lung Cancer. 2022 Apr;166:205-220. oi: 10.1016/j.lungcan.2022.03.008. Epub 2022 Mar 9.
18. Pelicon V, Cufer T, Knez L. Real-world outcomes of immunotherapy with or without chemotherapy in first-line treatment of advanced non-small cell lung cancer. Front Oncol. 2023 Jun 19;13:1182748. doi: 10.3389/fonc.2023.1182748.
19. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S et al; RECIST working group. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152. doi: 10.1016/S1470-2045(17)30074-8. Epub 2017 Mar 2. Erratum in: Lancet Oncol. 2019 May;20(5):e242. doi: 10.1016/S1470-2045(19)30240-2. Erratum in: Lancet Oncol. 2019 May;20(5):e242.
20. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the Common Terminology Criteria for Adverse Events (CTCAE – Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies. Actas Dermosifiliogr (Engl Ed). 2021 Jan;112(1):90-92. doi: 10.1016/j.ad.2019.05.009. Epub 2020 Sep 3.
21. Tateishi K, Mizugaki H, Ikezawa Y, Morita R, Yokoo K, Sumi T, Aso M, Kikuchi H, Nakamura A, Sekikawa M, Yoshiike F, Kitamura Y, Kimura N, Hachiya T, Tsurumi K, Agatsuma T, Megumi F, Nakamura K, Jingu D, Yamamoto H, Kosaka M, Yokouchi H. Real-world data of first-line treatment with pembrolizumab for NSCLC with high PD-L1 expression in elderly patients: a subgroup analysis of HOT/NJLCG2001.

Jpn J Clin Oncol. 2025 Mar 5;55(3):253-60. doi: 10.1093/jjco/hyae168.Tateishi K, Mizugaki H, Ikezawa Y, Morita R, Yokoo K, Sumi T et al. Real-world data of first-line treatment with pembrolizumab for NSCLC with high PD-L1 expression in elderly patients: a subgroup analysis of HOT/NJLCG2001. Jpn J Clin Oncol. 2024 Dec 4:hyae168.

22. Velcheti V, Hu X, Li Y, El-Osta H, Pietanza MC, Burke T. Real-World Time on Treatment with First-Line Pembrolizumab Monotherapy for Advanced NSCLC with PD-L1 Expression ≥ 50%: 3-Year Follow-Up Data. Cancers (Basel). 2022 Feb 18;14(4):1041. doi: 10.3390/cancers14041041.
23. Cafaro A, Foca F, Nanni O, Chiumente M, Coppola M, Russi A et al. Real-World Safety and Outcome of First-Line Pembrolizumab Monotherapy for Metastatic NSCLC with PDL-1 Expression ≥ 50%: A National Italian Multicentric Cohort ("PEMBROREAL" Study). Cancers (Basel). 2024 May 8;16(10):1802. doi: 10.3390/cancers16101802.
24. Ikezawa Y, Morita R, Mizugaki H, Tateishi K, Yokoo K, Sumi T et al. Real-world first-line treatment with pembrolizumab for non-small cell lung carcinoma with high PD-L1 expression: Updated analysis. Cancer Med. 2024 Jul;13(14):e70036. doi: 10.1002/cam4.70036.
25. Liguori L, Giorgio G, Polcaro G, Pagliara V, Malandrino D, Perri F et al. Checkpoint based immunotherapy in non-small cell lung cancer: a real-world retrospective study. Front Immunol. 2024 Nov 27;15:1419544. doi: 10.3389/fimmu.2024.1419544.
26. Bérard G, Guévremont C, Marcotte N, Schroeder C, Bouchard N, Rajan R; Programme de Gestion Thérapeutique des Médicaments (PGTM). Descriptive Analysis of First-Line Non-Small Cell Lung Cancer Treatment with Pembrolizumab in Tumors Expressing PD-L1 ≥ 50% in Patients Treated in Quebec's University Teaching Hospitals (DALP-First Study). Curr Oncol. 2023 Mar 11;30(3):3251-3262. doi: 10.3390/curroncol30030247.
27. Hektoen HH, Tsuruda KM, Fjellbirkeland L, Nilssen Y, Brustugun OT, Andreassen BK. Real-world evidence for pembrolizumab in non-small cell lung cancer: a nationwide cohort study. Br J Cancer 132, 93–102 (2025). doi: 10.1038/s41416-024-02895-1. Epub 2024 Nov 3.
28. Velcheti V, Rai P, Kao YH, Chirovsky D, Nunes AT, Liu SV. 5-Year Real-World Outcomes With Frontline Pembrolizumab Monotherapy in PD-L1 Expression ≥ 50% Advanced NSCLC. Clin Lung Cancer. 2024 Sep;25(6):502-508.e3. doi: 10.1016/j.cllc.2024.05.002. Epub 2024 May 16.
29. Njavro A, Murgić J, Jakšić B, Prpić M, Prgomet Sečan A, Franceschi D et al. Biomarkers and personalized medicine in prostate cancer – advent of precision oncology in (radio) therapy decision-making // Acta clinica Croatica. Supplement, 63 (2024), S2; 71-76. doi: 10.20471/acc.2022.61.s4.8
30. Qin D. Next-generation sequencing and its clinical application. Cancer Biol Med. 2019 Feb;16(1):4-10. doi: 10.20892/j.issn.2095-3941.2018.0055.
31. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M et al; CheckMate 026 Investigators. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Jun 22;376(25):2415-2426. doi: 10.1056/NEJMoa1613493.
32. Theelen WSME, Baas P. Pembrolizumab monotherapy for PD-L1 ≥50% non-small cell lung cancer, undisputed first choice? Ann Transl Med. 2019 Jul;7(Suppl 3):S140. doi: 10.21037/atm.2019.06.35.
33. Macioch T, Krzakowski M, Gołębiewska K, Dobek M, Warchałowska N, Niewada M et al. Pembrolizumab monotherapy survival benefits in metastatic non-small-cell lung cancer: a systematic review of real-world data. Discov Oncol. 2024 Jul 24;15(1):303. doi: 10.1007/s12672-024-01153-3.
34. Sun L, Bleiberg B, Hwang WT, Marmarelis ME, Langer CJ, Singh A et al. Association Between Duration of Immunotherapy and Overall Survival in Advanced Non-Small Cell Lung Cancer. JAMA Oncol. 2023 Aug 1;9(8):1075-1082. doi: 10.1001/jamaoncol.2023.1891.
35. Shah M, Marmarelis ME, Mamtani R, Hennessy S. Association Between Survival and Very High Versus High PD-L1 Expression in Patients Receiving Pembrolizumab as First-line Treatment for Advanced Non-Small Cell Lung Cancer. Clin Lung Cancer. 2022 Dec;23(8):731-736. doi: 10.1016/j.cllc.2022.07.003. Epub 2022 Jul 22.
36. Aguilar EJ, Ricciuti B, Gainor JF, Kehl KL, Kravets S, Dahlberg S et al. Outcomes to first-line pembrolizumab in patients with non-small-cell lung cancer and very high PD-L1 expression. Ann Oncol. 2019 Oct 1;30(10):1653-1659. doi: 10.1093/annonc/mdz288.
37. Shah M, Hubbard RA, Mamtani R, Marmarelis ME, Hennessy S. Very high PD-L1 expression as a prognostic indicator of overall survival among patients with advanced non-small cell lung cancer receiving anti-PD-(L)1 monotherapies in routine practice. Pharmacoepidemiol Drug Saf. 2022 Oct;31(10):1121-1126. doi: 10.1002/pds.5487. Epub 2022 Jun 22.

38. Silberg M, Krabbe LM, Bögemann M, Schrader AJ, Tully K, Schlack K. Immune-Related Adverse Events Can Predict Progression-Free and Overall Survival In Patients With Metastatic Renal Cell Carcinoma Treated With Immune Checkpoint Inhibitors. Clin Genitourin Cancer. 2024 Oct;22(5):102164. doi: 10.1016/j.clgc.2024.102164. Epub 2024 Jul 17.
39. Cook S, Samuel V, Meyers DE, Stukalin I, Litt I, Sangha R et al. Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors. JAMA Netw Open. 2024 Jan 2;7(1):e2352302. doi: 10.1001/jamanetworkopen.2023.52302.
40. Manson G, Maria ATJ, Poizeau F, Danlos FX, Kostine M, Brosseau S et al. Worsening and newly diagnosed paraneoplastic syndromes following anti-PD-1 or anti-PD-L1 immunotherapies, a descriptive study. J Immunother Cancer. 2019 Dec 3;7(1):337. doi: 10.1186/s40425-019-0821-8.

Sažetak

KLINIČKI ISHODI BOLESNIKA S UZNAPREDOVALIM NESITNOSTANIČNIM KARCINOMOM PLUĆA S VISOKOM EKSPRESIJOM PD-L1 (≥ 50%) LIJEČENIH MONOTERAPIJOM PEMBROLIZUMABOM: ISKUSTVO KLINIČKOG BOLNIČKOG CENTRA U SREDNJOJ EUROPI

Jasmina Marić Brozić, *Hrvoje Brčić*, *Klara Brčić*, *Kristina Urch*, *Neva Purgar Levarda*, *Jasna Radić* i *Ana Fröbe*

Pembrolizumab, inhibitor imunološke kontrolne točke PD-1, pokazao je učinkovitost u vidu duljeg preživljenja kao samostalna terapija u kliničkim ispitivanjima za uznapredovali nesitnostanični karcinom pluća (eng. kratica NSCLC) s visokom ekspresijom PD-L1 (≥ 50%).

Proveli smo retrospektivno istraživanje u Kliničkom bolničkom centru Sestre milosrdnice u Zagrebu kako bismo analizirali ishode bolesnika s uznapredovalim NSCLC-om (stadij IIIB-IV) i visokom ekspresijom PD-L1, koji su primali pembrolizumab u monoterapiji između ožujka 2018. i ožujka 2023. Istraživanje je obuhvatilo demografske i kliničke podatke, uključujući odgovor na liječenje, nuspojave, preživljenje bez progresije bolesti (eng. PFS) i ukupno preživljenje (eng. OS). Podatke smo analizirali pomoću deskriptivne statistike, Kaplan-Meierove metode preživljenja te multivarijatne Coxove regresije.

U istraživanje su uključena 72 bolesnika, a medijan praćenja bio je 49 mjeseci. Medijan preživljenja bez progresije bolesti iznosio je 13 mjeseci (95% CI: 5-20 mjeseci), dok je medijan ukupnog preživljenja iznosio 24 mjeseca (95% CI: 14-46 mjeseci). Jednogodišnja stopa preživljenja iznosila je 66,67 %. Nuspojave su bile u skladu s onima zabilježenima u kliničkim ispitivanjima.

Ova studija potvrđuje učinkovitost i sigurnost pembrolizumaba kao samostalne terapije za uznapredovali NSCLC s visokom ekspresijom PD-L1 u stvarnoj kliničkoj praksi. Dobiveni rezultati preživljenja u skladu su s podacima iz kliničkih ispitivanja.

Ključne riječi: *Pembrolizumab; NSCLC; PD-1; PD-L1; Imunoterapija*