European Review for Medical and Pharmacological Sciences 2023; 27: 9213-9225

Real-world data on efficacy and safety of pembrolizumab in the first-line treatment of metastatic lung cancer in patients with PD-L1 expression >0% – a single center experience

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Abstract. – OBJECTIVE: With the advent of immunotherapy, there has been a significant improvement in the outcomes of non-small cell lung cancer treatment. Several clinical trials have confirmed the efficacy and safety of pembrolizumab, but research with real-world data is needed to confirm the findings from clinical trials.

PATIENTS AND METHODS: In this retrospective study, data on the treatment of lung cancer with pembrolizumab were analyzed in 78 patients who started pembrolizumab therapy as first-line treatment for metastatic disease at University Hospital Centre Osijek, from May 15, 2018, until December 31, 2021. November 30, 2022, was set as the last date of data monitoring. Patients who had received less than 3 cycles of pembrolizumab were excluded from the study. The main objectives of the study were OS (overall survival) and PFS (progression-free survival). The differences in the incidence and type of adverse events between the two groups of patients were also compared.

RESULTS: Kaplan-Meier analysis of the survival determined that the median OS was 20 months and PFS was 13 months. Although OS and PFS are longer in patients with PD-L1 (programmed death-ligand 1) ≥ 50%, the differences are not statistically significant. The most commonly reported adverse events related to pembrolizumab treatment were gastrointestinal adverse events. No significant differences were found in the frequency of occurrence of certain adverse events between the two groups of patients.

CONCLUSIONS: This study demonstrates that real-world data for pembrolizumab treatment of non-small cell lung cancer confirm the efficacy and safety indicated by clinical trials. Nevertheless, it is necessary to assess the patient's general condition more objectively before starting the treatment.

Key Words:
Lung cancer, Pembrolizumab, Overall survival, Progression-free survival.

Introduction

Despite the great progress of modern oncology, lung cancer, with regard to epidemiological data worldwide, remains the leading subject of research into new treatment options. Namely, according to data from the Global Cancer Observatory (GLOBOCAN) from 2020, lung cancer is still the 1st cancer in the world in terms of mortality, with as many as 1.8 million deaths, and is the cause of 18% of cancer-related deaths[1,2]. In Croatia, lung cancer is the 4th in incidence, behind breast, prostate, and colorectal cancer[2]. It is known that smoking is still the leading risk factor for lung cancer[3]. Looking at gender as a risk factor for lung cancer, according to data from the past decade, the frequency is decreasing in the male population and increasing in the female population[3].

The basic classification of lung cancer is into small cell and non-small cell lung cancer, and it is known that non-small cell lung cancer is a much more common form of the disease with better treatment outcomes and overall survival[4]. Histo-

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logically, we differentiate squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and NOS (non-otherwise specified) type[5].

When talking about the treatment of non-small cell lung cancer, the therapeutic options in the early stages include surgery, chemotherapy, and radiotherapy. However, a turning point in the treatment of metastatic non-small cell lung cancer was marked by the possibility of identifying certain tumor cell mutations [for example, EGFR (epidermal growth factor receptor), ALK (anaplastic lymphoma kinase), ROS1 (ROS proto-oncogene 1)] and the possibility of measuring the expression of certain molecules on tumor cells, such as the PD-L1 (programmed death-ligand 1) molecule. Consequently, the advent of targeted therapy and immunotherapy has changed the paradigm of treatment of metastatic non-small cell lung cancer. We consider the most important immunotherapy drugs for the treatment of cancer to be checkpoint inhibitors, which are monoclonal antibodies in their composition[6]. It has long been thought that the human immune system, and especially T-lymphocytes, can represent a target system in the fight against cancer. Checkpoint inhibitors, which include CTLA4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (programmed death-1)/PD-L1 inhibitors, act precisely on the immune response associated with T-lymphocytes[6]. Blockade of PD-1 and PD-L1 molecules is the area of interest of this research. The most important PD-1 inhibitors include nivolumab, cemiplimab, and pembrolizumab, while the PD-L1 inhibitors include durvalumab, avelumab, and atezolizumab[6,7]. The interaction of the PD-1 receptor on the surface of T-lymphocytes and its ligand, the PD-L1 molecule, on tumor cells disables the normal biological function of T-lymphocytes and causes their apoptosis. This allows the tumor to escape the cytotoxic action of the immune system[8]. By blocking this interaction, tumor cells become susceptible to destruction by the immune system[8].

The PD-1 inhibitor pembrolizumab has brought a revolution in the treatment of numerous cancers. Due to the excellent results of clinical studies, it is being approved every day in more and more indications around the world. In Croatia, pembrolizumab is approved for the treatment of non-small cell lung cancer and is available as monotherapy (in patients with expression of the PD-L1 molecule from 50% to 100%) or in combination with chemotherapy (in patients with PD-L1 expression 0% and expression 1-49%) as first-line treatment for metastatic disease.

It is important to mention several clinical trials that allowed pembrolizumab to become the standard of care in the treatment of metastatic non-small cell lung cancer. The KEYNOTE-001 phase Ib clinical trial is the first study to evaluate the efficacy of pembrolizumab treatment in advanced non-small cell lung cancer[9]. The trial included 2 basic groups of patients. One group received at least one previous line of treatment for metastatic disease, while for the other group, pembrolizumab monotherapy represented first-line treatment[9]. The most important results of this trial are twofold. Firstly, the five-year overall survival was 23.2% for patients without prior treatment and 15.5% for patients who received pembrolizumab as first-line treatment[9]. Secondly, the five-year overall survival in patients with PD-L1 molecule expression equal to or greater than 50%, which was 29.6% in patients for whom pembrolizumab was first-line treatment compared to 25.0% in patients for whom it was not[9]. In this study, pembrolizumab was also shown to have a good safety profile[9].

The phase III clinical trial KEYNOTE-042 demonstrated significantly better overall survival in patients treated with pembrolizumab compared to patients treated with platinum-based chemotherapy in all patient groups[10]. In one group the expression of the PD-L1 molecule was from 1% to 19%, in the other, from 20% to 49%, and in the third, from 50% to 100%[10]. In high expressors of the PD-L1 molecule (50% and more) treated with pembrolizumab, the KEYNOTE-024 phase III clinical trial[11] demonstrated significantly better overall survival and progression-free survival compared to the group of patients treated with platinum-based chemotherapy. Furthermore, two additional clinical trials showed the efficacy of pembrolizumab treatment in combination with chemotherapy depending on tumor histology, independent of PD-L1 expression. The KEYNOTE-407 clinical trial focused on squamous metastatic NSCLC (non-small cell lung cancer) and showed significantly better overall survival and time to disease progression in patients treated with pembrolizumab plus carboplatin chemotherapy plus paclitaxel or nab-paclitaxel compared to a group of patients treated only with chemotherapy plus placebo[12]. KEYNOTE-189 is a clinical trial[13] that demonstrated significantly better overall survival and time to disease progression in patients with non-squamous metastatic lung cancer treated with pembrolizumab plus platinum-based chemotherapy and pemetrexed compared to a group of patients treated only with chemothera-

py plus placebo. In this study, patients received platinum-based chemotherapy (cisplatin or carboplatin) in addition to pemetrexed for 4 cycles and then continued to receive pemetrexed alone as maintenance therapy[13]. Despite numerous existing clinical trials, the question of whether chemotherapy should be added to the treatment of patients with PD-L1 expression equal to or greater than 50% remains unresolved. However, if we compare the clinical trials KEYNOTE-024 and KEYNOTE-189, in patients with PD-L1 expression equal to or greater than 50%, no significant differences in overall survival are found (1-year overall survival in KEYNOTE-024 of 70% compared to that in KEYNOTE-189 of 73%)[14]. This knowledge, along with the fact that chemotherapy contributes to the toxicity of the overall treatment, speaks in favor of the fact that in high PD-L1 expressors, the first choice of therapy should be pembrolizumab monotherapy. Considering the lack of head-to-head studies in which the effectiveness of two drugs would be compared, meta-analyses are to be regarded as an extremely important means of confirming the effectiveness of drugs. According to one meta-analysis of several clinical trials, pembrolizumab in combination with chemotherapy showed the highest efficacy compared to the other investigated immune checkpoint inhibitors and the highest efficacy in almost all PD-L1 subgroups[15]. Furthermore, in a meta-analysis that included cohorts from 5 clinical trials and focused on restricted mean survival time, pembrolizumab was shown to be the most effective immune checkpoint inhibitor[16].

Since all the above-mentioned clinical trials and meta-analyses have shown a significant effectiveness in the treatment of metastatic non-small cell lung cancer with pembrolizumab in monotherapy or in combination with chemotherapy, it is crucial to monitor the results of this treatment in the future, in different centers around the world. Correspondingly, an analysis of the results of such treatment was also done at University Hospital Centre Osijek, based on real-world data.

Patients and Methods

In this retrospective study, data on the treatment of lung cancer with pembrolizumab were analyzed in 78 patients who started pembrolizumab therapy as first-line treatment for metastatic disease at University Hospital Centre Osijek from May 15, 2018, until December 31, 2021. November 30, 2022, was set as the last date of data monitoring. The research was approved by the Ethics Committee of University Hospital Centre Osijek (number of acceptance: R1-4012/2023) and was carried out in accordance with all the principles of the Declaration of Helsinki, with patient anonymity and data confidentiality maintained. Informed consent was not obtained from participants included in the study because data were collected retrospectively from the archive and the information system of University Hospital Centre Osijek.

Inclusion and Exclusion Criteria

One of the inclusion criteria was the age of participants, which required them to be 18 years of age or older. The other inclusion criterion was being eligible for treatment with pembrolizumab as first-line treatment for metastatic non-small cell lung cancer, i.e., meeting the following criteria – ECOG PS (Eastern Cooperative Oncology Group performance status) 0-1, negative status of activating mutations EGFR, ALK, ROS1 (depending on tumor histology), absence of autoimmune diseases and corticosteroids or immunosuppressants in permanent therapy, and PD-L1 molecule expression >1%. The exclusion criteria were the duration of treatment with pembrolizumab, if shorter than 3 treatment cycles, i.e., shorter than 6 weeks, and negative expression of PD-L1 (<1%).

Collected patient data included year of birth (age), gender, ECOG PS, smoking status, comorbidities, and lastly, data related to lung cancer treatment – date of diagnosis, method of diagnosing the disease, stage of the disease at the time of diagnosis, histological type of tumor, status of activating mutations, the expression level of the PD-L1 molecule, and data on therapies that were possibly performed before or after pembrolizumab therapy (these include neoadjuvant treatment, operative treatment, adjuvant treatment, radiotherapy, second and further lines of treatment for metastatic disease). Collected data related to treatment with pembrolizumab as first-line treatment for metastatic disease included following information – site of metastasis, date of the first and last dose of pembrolizumab, number of pembrolizumab cycles, chemotherapy protocol with which patients received pembrolizumab (if they received it along with chemotherapy), adverse events of treatment, and the first evaluation since the start of treatment with pembrolizumab.

All patients included in the study received pembrolizumab intravenously at a dose of 200 mg per cycle every 3 weeks until radiological-

ly determined disease progression, unacceptable toxicity, or death. After every 3 cycles of treatment, CT (computed tomography) evaluation of the thorax, abdomen, and pelvis was performed. For the purposes of analyzing the research objectives, patients were divided into 2 groups according to PD-L1 expression – one group of subjects had PD-L1 expression 1-49%, and the other 50% and more. The main objectives of this study were OS (overall survival; time from the first dose of pembrolizumab to the last control or death) and PFS (progression-free survival; time from the first dose of pembrolizumab to established disease progression, the last control or death). It was also checked whether there was a significant difference in the number and type of adverse events during treatment with pembrolizumab between the above-mentioned two groups of patients and whether there was a difference in the representation of individual metastases.

Statistical Analysis

Categorical data are represented by absolute and relative frequencies. Categorical data differences were tested with Fisher's exact test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. Numerical data are described by the median and the limits of the interquartile range (IQR). Kaplan-Meier survival curves were compared using the log-rank test. All *p*-values are two-sided. The significance level was set at Alpha (α) = 0.05. For statistical analysis, the statistical programs MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2023) and SPSS v. 23 (IBM Corp., Armonk, NY, USA) were used.

Results

Basic Characteristics of Patients and Cancer Histology

The research was conducted on a sample of 78 patients. The sample consisted of 45 (58%) men and 33 (42%) women (Table I). At the beginning of treatment with pembrolizumab, most of the patients, 61 (78%) of them, had ECOG status 0, and almost half of them, 33 (47%), were smokers (Table I). Arterial hypertension was singled out as the most common comorbidity among the patients (Table I). The age of the patients ranged from a minimum of 45 to a maximum of 83 years, with a median of 63 years (Table I).

Looking at the histological classification of lung cancer, more than half of the patients, 55 of them (71%), had adenocarcinoma (Table I). During the period of time that was inspected for the purposes of this study, the majority of lung cancers were proven at our institution in a cytological smear, or a cell block made from that same cytological smear (Table I). We can see that, unfortunately, the largest number of cancers were diagnosed in the 4th stage of the disease (Table I). PD-L1 expression equal to 50% or greater was found in 46 (59%) patients, while the median PD-L1 was 55 (IQR 20-80), ranging from a minimum of 1 to a maximum of 100 (Table I).

Data on the Treatment of Early Detected Lung Cancer

In 14 patients, lung cancer was detected in the second or third stage, and 12 (86%) of them were operated on (Table I). The most frequently applied adjuvant chemotherapy protocol was cisplatin plus pemetrexed, which was received by 3 patients, followed by PC (carboplatin plus paclitaxel) and GC (gemcitabine and cisplatin) protocols, while only one patient received adjuvant PE protocol (cisplatin and etoposide). If we look at the response to adjuvant treatment, 4 patients, or exactly half, did not have a relapse of the disease, while progression was observed in the other half.

First-Line Treatment of Metastatic Non-Small Cell Lung Cancer

When examining the representation of certain sites of metastases at the beginning of treatment with pembrolizumab, we observed that more than half of the patients, a total of 40 (51%), had lung metastases, while the smallest number of patients had liver metastases (Table II). However, there was no statistically significant difference between the representation of certain sites of metastasis between the two groups of patients (Table II).

Patients who received chemotherapy with pembrolizumab most often received cisplatin with pemetrexed, 29 (91%) of them, and only 3 (9%) patients received paclitaxel and carboplatin. The median number of cycles of pembrolizumab in the group of patients with PD-L1 1-49% was 12 cycles (IQR 6-21), while in the group of patients with PD-L1 equal to or greater than 50%, it was 14.5 cycles (IQR 6.8-25.8). Although the median number of cycles in the second group is higher, there was no significant difference between the two results (Mann-Whitney U test, p=0.53). The median of treatment with pembrolizumab in the

group of patients with PD-L1 1-49% was 10.3 months (IQR 4.4-19.4), and in the group of patients with PD-L1 equal to or greater than 50%, it was 10.1 months (IQR 5-18.2), with no significant difference between the groups (Mann-Whitney U test, p=84).

The most common response to treatment with pembrolizumab in the first evaluation after 3 cycles of treatment is partial response, followed by stable disease (Table III). The biggest difference is visible in pseudoprogression, which is visibly more frequent in patients with PD-L1 50% or higher, but without a statistically significant difference (Table III). The research involved a larger sample of patients, it is possible that a statistically significant difference would have been reached in these results.

Table I. Basic characteristics of patients and cancer histology.

Sex	
Male	45 (58)
Female	33 (42)
ECOG status	
0	61 (78)
0-1	10 (13)
1	7 (9)
Age at diagnosis [Median (IQR)]	63 (60-68)
Smoking status	
No	6 (8)
Yes	37 (47)
Former smoker	13 (17)
Unknown	22 (28)
Comorbidities	
COPD	11 (11)
Hypertension	29 (37)
Diabetes mellitus	13 (17)
Other comorbidities	42 (54)
Histology	
Adenocarcinoma	55 (71)
Adenosquamous carcinoma	1 (1)
Squamous carcinoma	10 (13)
NOS type	8 (10)
Poorly differentiated	4 (5)
Sample type	
Cytological smear or a cell block	45 (58)
Transthoracic punction or biopsy	17 (22)
Intraoperative biopsy	10 (13)
Intraoperative biopsy of metastases	6 (8)
Stage at diagnosis	
II	6(8)
III	8(10)
IV	64 (82)
PD-L1 [Median (IQR)]	55 (20-80)
PD-L1	
1-49%	32 (41)
≥50%	46 (59)

The most commonly reported adverse events related to pembrolizumab treatment in our research were gastrointestinal adverse events, particularly decreased appetite and diarrhea (Table IV). In other groups of adverse events and disorders of blood tests, the most common were anemia (8 patients), increased transaminases (9 patients), dyspnea (8 patients), hypothyroidism (8 patients), and fatigue (10 patients) (Table IV). No significant differences were found in the frequency of certain adverse events between the two groups of patients with different PD-L1 expressions (Table IV). In our sample, no patient had a dose reduction of pembrolizumab, and 7 (9%) patients had temporary or permanent discontinuation of therapy due to unacceptable toxicity.

Further Lines of Treatment and Radiotherapy

A total of 18 patients received second-line treatment of metastatic disease after progression to pembrolizumab. Cisplatin with pemetrexed (8 patients) was the most commonly used protocol in second-line treatment, followed by docetaxel and nintedanib (7 patients). Two patients received pemetrexed as monotherapy, and one patient received cisplatin with etoposide. The most common response to chemotherapy in second-line treatment after the 1st evaluation was a partial response in 5 (28%) patients, followed by stable disease demonstrated in 4 (22%) patients and disease progression in 3 (17%) patients. A total of 8 patients received third and further lines of treatment. Out of the total number of patients in our sample, 33 (42%) patients underwent radiotherapy, which was palliative in 26 (79%) patients (Table V). Out of the total number of irradiated patients, only 4 (12%) had their primary tumor irradiated (Table V). The most common metastatic site of radiation was brain metastases (Table V). No statistically significant differences were found in the frequency of radiotherapy between the observed groups of patients (Table V).

When we look at the final outcome of the treatment on the last observed date, 35 (45%) patients were still alive. Of those 30 patients who were still alive on the last observed date, 20 of them (57%) belonged to the PD-L1 expression group 50% and more, and 15 (43%) to the PD-L1 expression group 1-49%.

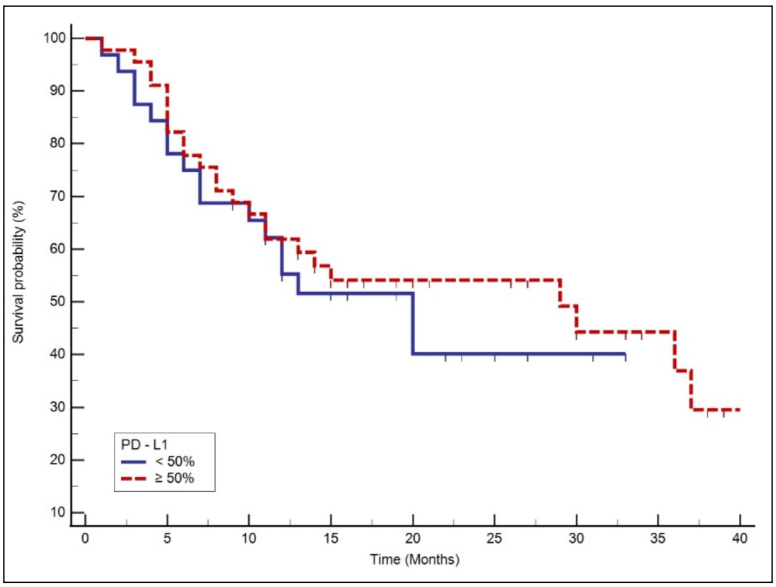

Figure 1. Kaplan Meier curve of overall survival (OS) in relation to PD-L1.

Survival (Kaplan-Meier)

Kaplan-Meier analysis of the survival of the observed patients determined that the median overall survival was 20 months [95% CI (confidence interval) from 11 to 37) (Table VI, Figure 1)]. Although 1-year, 2-year, and 3-year survival is longer in patients with PD-L1≥ 50%, the differences are not statistically significant (Table VI, Figure 1). Looking at one-year overall survival, the median was not reached in either group of patients, which means that more than 50% of patients were alive one year after receiving the 1st dose of pembrolizumab (Table VI). The median was also not reached in 2-year overall survival for the group of patients with PD-L1 ≥ 50% (Table VI).

Kaplan-Meier analysis of the survival of the observed patients determined that the overall median time to disease progression (PFS) was 13 (95% CI, from 9 to 23) months (Table VII, Figure 2). It is observed that the time to disease progression is longer in patients with PD-L1≥ 50%, but without a statistically significant difference (Table VII, Figure 2).

Discussion

Strengths and Limitations

The results of our study, looking at the primary goals – OS and PFS, show excellent effectiveness of pembrolizumab in real clinical practice, but certain limitations of the study should be taken into account. Clinical trials on the treatment of metastatic lung cancer with pembrolizumab had very strict inclusion criteria, for example, ECOG PS 0-1.

In our study, one of the exclusion criteria was receiving less than 3 cycles of pembrolizumab. This fact can be considered a limitation of our study. Namely, despite its importance in the evaluation of an oncology patient, ECOG PS is still a subjective parameter that depends on the physician's personal assessment. This fact was taken into consideration by other researchers around the world, noting that two doctors can evaluate the same patient's ECOG PS differently, due to the fact that ECOG PS does not take into account numerous parameters, such as age, comorbidities, the possible presence of polypharmacy, etc[17]. In the study that included 88 patients with different ECOG PS, Jiménez Galan et al[17] state that as many as 25% of patients died or progressed before the first evaluation of the disease[17]. In our sample, all patients were ECOG PS 0-1, while in the aforementioned Spanish study, this was the case in 63.7% of patients[17]. The median age was very similar. In our sample, it was 63 (45-83), and in the aforementioned study, it was 66 (46-85)[17]. The overall OS of our sample independent of PD-L1 expression, which was 20 months (95% CI: 11-37), is similar to the overall OS of the mentioned study in the group of ECOG PS 0-1 subjects, which was 18.9 months (95% CI: 11-96.0)[17].

Table II. Localization of metastases at the beginning of treatment with pembrolizumab.

Localization of metastases	Number (%) of patients according to PD-L1			*p**
	1-49%	≥ 50%	Total	
Lung metastases	17 (53)	23 (50)	40 (51)	0.82
Lymph node metastases	17 (53)	22 (48)	39 (50)	0.81
Liver metastases	3 (9)	5 (11)	8 (10)	>0.99
Brain metastases	6 (19)	12 (26)	18 (23)	0.59
Bone metastases	7 (22)	8 (17)	15 (19)	0.77
Adrenal gland metastases	7 (22)	13 (28)	20 (26)	0.60
Rare sites of metastases (cutis, renis, lienalis, cerebelli, colli, pancreatis)	2 (6)	7 (15)	9 (12)	0.30
Pleural metastases/malignant pleural effusion	6 (19)	7 (15)	13 (17)	0.76

*Fisher's exact test.

Table III. First evaluation since the beginning of treatment with pembrolizumab.

Localization of metastases	Number (%) of patients according to PD-L1			*p**
	1-49%	≥ 50%	Total	
CR (complete response)	0	1 (2)	1 (1)	
PR (partial response)	13 (42)	15 (36)	28 (38)	
SD (stable disease)	14 (45)	12 (29)	26 (36)	
Disease progression	0	2 (5)	2 (3)	
Pseudoprogression	2 (6)	11 (26)	13 (18)	
Mixed response	2 (6)	1 (2)	3 (4)	

*Fisher's exact test.

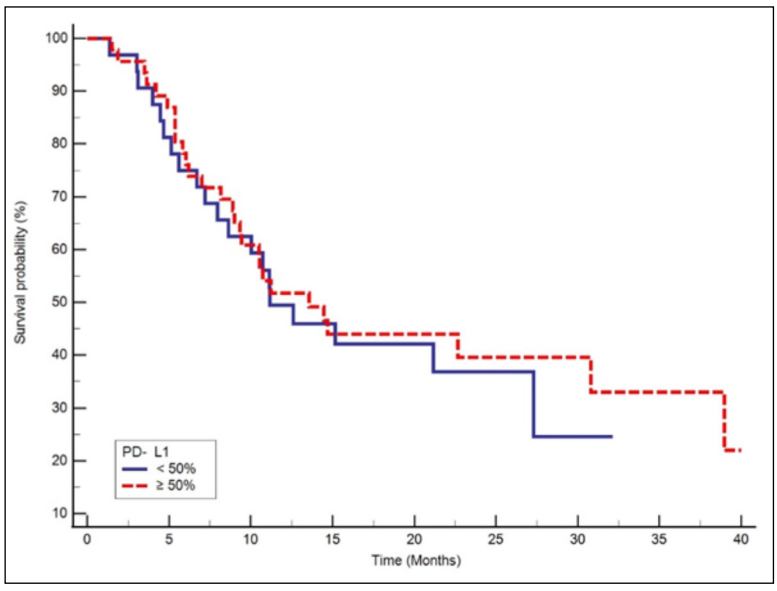

Figure 2. Kaplan Meier survival curve with regard to progression in relation to PD-L1.

Table IV. Adverse events of pembrolizumab treatment.

Localization of metastases	Number (%) of patients according to PD-L1			*p**
	1-49%	≥ 50%	Total	
Blood and lymphatic system disorders	7 (19)	5 (11)	12 (14)	0.35
Neutropenia	3/7	0	3/12	0.21
Anemia	5/7	3/5	8/12	>0.99
Thrombocytopenia	2/7	4/5	6/12	0.24
Leukopenia	1/7	0	1/12	>0.99
Pancytopenia	1/7	0	1/12	>0.99
Disorders of other blood tests	6 (19)	9 (17)	15 (18)	>0.99
Increase in the level of transaminases	3/6	6/9	9/15	0.62
Increase in the level of creatinine	3/9	3/9	6/15	0.62
Skin disorders	2 (6)	9 (20)	11 (14)	0.11
Rash	2/2	2/9	4/11	0.11
Pruritus	0	3/9	3/11	>0.99
Eczema	0	2/9	2/11	>0.99
Alopecia	0	1/9	1/11	>0.99
Other skin adverse events	0	2/9	2/11	>0.99
Cardiac disorders	1 (3)	3 (4)	4 (4)	0.63
Rare adverse events	1/1	3/3	4/4	-
Respiratory, thoracic and mediastinal disorders	4 (10)	9 (16)	13 (13)	0.39
Dyspnea	4/4	4/6	8/11	0.11
Cough	0	2/6	2/11	>0.99
Pneumonitis	0	5/6	5/11	0.11
Nervous system disorders	2 (5)	2 (4)	4 (4)	>0.99
Headache	1/1	1/2	2/3	>0.99
Peripheral neuropathy	1/1	1/2	2/3	>0.99
Endocrine disorders	5 (12)	7 (13)	12 (16)	>0.99
Hypothyroidism	2/5	6/7	8/12	0.22
Hyperthyroidism	0	1/7	1/12	>0.99
Adrenal insufficiency	2/5	0	2/12	0.15
Hypophysitis	1/5	0	1/12	0.42
Gastrointestinal disorders	12 (29)	12 (21)	24 (25)	0.48
Diarrhea	3/12	4/12	7/24	>0.99
Constipation	1/12	2/12	3/24	>0.99
Decreased appetite	5/12	5/12	10/24	>0.99
Nausea	3/12	1/12	4/24	0.59
Abdominal pain	0/12	2/12	2/24	0.48
Other adverse events	7 (17)	11 (20)	18 (18)	0.80
Myositis	0/7	1/11	1/18	>0.99
Hepatitis	0/7	5/11	5/18	0.10
Fatigue	6/7	4/11	10/18	0.07
Other less common adverse events	1/7	2/11	3/18	>0.99

*Fisher's exact test.

Therefore, it is legitimate to assume that even in our patients who received less than 3 cycles of pembrolizumab, death or disease progression occurred due to clinical parameters that were not taken into account by the ECOG PS assessment. Had the general condition of these patients been assessed with a tool that ensures more objectivity than the ECOG PS assessment does, it might have been noticed earlier that the patients were not eligible candidates for immunotherapy. Hence, it is necessary to create a new standardized test that would assess the general condition of patients in more detail. In addition, it would be of great benefit to clinical practice if more clinical trials were conducted on patients with a poor general condition. Such results would provide a new perspective on the effectiveness of certain drugs.

Comparison with Clinical Trials

It is difficult to extrapolate data from clinical trials to results from actual clinical practice, but taking into consideration certain limitations of

our research, we can conclude that our results confirm the effectiveness and safety of pembrolizumab in the treatment of lung cancer. In the KEYNOTE-024 (ClinicalTrials.gov identifier: NCT02142738) trial[11], 154 patients receiving pembrolizumab with PD-L1 expression ≥ 50% were included, while in our sample 46 patients had PD-L1 ≥ 50%. The large difference in sample size is one of the possible causes of the inconsistent results. In the study analysis at a median follow-up of 25.2 months, the median OS was 30 months (95% CI: 18.3 to not reached), and in the 5-year analysis, it was 26.2 months (95% CI: 18.3-40.4)[11,18]. The overall median of OS in the same group of patients in our sample was 29 months (95% CI: 10-37), while it was not reached in one- and two-year overall survival analysis. When we compare the one-year survival in our study with the one in KEYNOTE-024 clinical trial analysis at a median follow-up of 11.2 months, it is observed that in both cases, the median OS was not reached[11]. In addition, in the 5-year analysis of the KEYNOTE-024 clinical trial, the median PFS was 7.7 months (95% CI: 6.1-10.2), and in our sample, it was 14 months (95% CI: 9-39)[18]. This fact suggests that PFS is higher in patients who received at least 3 cycles of pembrolizumab. It is likely that the PFS would have been much more similar to that in the clinical trial if our sample had been larger and if our study had included patients who had received less than 3 cycles of pembrolizumab.

In our study, patients were divided into groups according to PD-L1 expression, but not according to histology, considering the markedly smaller number of patients with squamous differentiation lung cancer. Clinical trial KEYNOTE-189 investigated non-squamous carcinoma and KEYNOTE-407 investigated squamous carcinoma[19,20]. Both had a subgroup of patients with PD-L1 expression of 1-49%. In the 5-year analysis of the KEYNOTE-189 trial (ClinicalTrials.gov identifier: NCT02578680), in the subgroup of patients with PD-L1 1-49%, OS was 21.8 months (95% CI: 17.7-25.6) and PFS was 9.4 months (95% CI: 8.1-13.8)[19]. Furthermore, in the 5-year analysis of KEYNOTE-407 (ClinicalTrials.gov identifier: NCT02775435), in the subgroup of patients with PD-L1 1-49%, OS was 18 months (95% CI: 13.6 to 22.8) and PFS was 8.2 months (95% CI: 6.2-11.4)[20]. Median OS in the group of patients with PD-L1 1-49% in our study was 20 months (95% CI: 7-20), and PFS was 11 months (95% CI: 7-27), which is in accordance with the results of the aforementioned clinical trials.

The patient demographic data on the median age, gender, and smoking status shown in the mentioned clinical trials and examples from real-world data completely coincide with ours – most of them were men, the median age was very similar, and the patients were mostly former or active smokers[17-20]. The safety profile of pembrolizumab in our research proved to be satisfactory, as well as in the aforementioned clinical trials. In the

Table V. Radiotherapy.

Localization of metastases	Number (%) of patients according to PD-L1			*p**
	1-49%	≥ 50%	Total	
Radiotherapy	13 (41)	20 (44)	33 (42)	0.82
Palliative radiotherapy	11 (85)	15 (75)	26 (79)	0.89
Curative radiotherapy (primary tumor)	1 (8)	3 (15)	4 (12)	
SBRT	0	1 (5)	1 (3)	
SRS	1 (8)	1 (5)	2 (6)	
Total	13 (100)	20 (100)	33 (100)	
Radiotherapy of metastases				
Brain metastases	8 (67)	11 (65)	19 (66)	>0.99
Bone metastases	3 (25)	4 (24)	7 (24)	
Lymph node metastases	1 (8)	1 (6)	2 (7)	
Rare sites of metastases (abdominal metastases)	0	1 (6)	1 (3)	
Total	12 (100)	17 (100)	29 (100)	

*Fisher's exact test.

Table VI. Overall survival.

	Number (%) of patients who died	Number (%) of living patients	Mean (95% CI)	Median (95% CI)	Logrank test (*p*)	Hazard ratio* (95% CI)
Overall survival	43 (55)	35 (45)	24 (19-28)	20 (11-37)		
One - year OS	30 (38)	48 (6a2)	29 (25-33)	-		
Two - year OS	38 (49)	40 (51)	26 (21-30)	20 (11-20)		
Three - year OS	42 (54)	36 (46)	23 (19-27)	20 (11-37)		
Overall survival						
PD-L1 1-49%	17 (53)	15 (47)	19 (14-23)	20 (7-20)	0.59	1.2
PD-L1 ≥ 50%	26 (57)	20 (43)	24 (19-30)	29 (10-37)		(0.62-2.29)
One - year OS						
PD-L1 1-49%	12 (38)	20 (63)	23 (17-27)	-	0.98	1.01
PD-L1 ≥ 50%	18 (39)	28 (61)	29 (24-35)	-		(0.48-2.12)
Two-year OS						
PD-L1 1-49%	17 (53)	15 (47)	19 (14-23)	20 (7-20)	0.51	1.3
PD-L1 ≥ 50%	21 (46)	25 (54)	27 (22-32)	-		(0.64-2.42)
Three-year OS						
PD-L1 1-49%	17 (53)	15 (47)	19 (14 – 23)	20 (7-20)	0.59	1.2
PD-L1 ≥ 50%	25 (54)	21 (46)	24 (19 – 30)	29 (10-37)		(0.62-2.29)

*Fisher's exact test.

meta-analysis mentioned above, pembrolizumab also showed a good safety profile, as it did in our study[15]. The most common adverse events in our studied sample were fatigue, decreased appetite, diarrhea, dyspnea, and anemia. The same adverse events were very common in clinical trials[18-20]. In

Table VII. Progression free survival.

	Number (%) of patients		Mean (95% CI)	Median (95% CI)	Logrank test (*p*)	Hazard ratio* (95% CI)
	Disease progression	Progression free				
Overall survival	48 (62)	30 (39)	21 (17-25)	13 (9-23)		
One - year OS	12 (15)	66 (84)	38 (34-41)	-		
Two - year OS	15 (19)	63 (81)	35 (30-39)	-		
Three - year OS	15 (19)	63 (81)	34 (29-39)	-		
PFS according to PD-L1						
PD-L1 1-49%	20 (63)	12 (38)	17 (13-21)	0.59	1.2	
PD-L1 ≥ 50%	28 (61)	18 (39)	22 (16-27)		(0.62-2.29)	
One - year PFS according to PD-L1						
PD-L1 1-49%	5 (16)	27 (84)	27 (23-31)	-	0.92	1.1
PD-L1 ≥ 50%	7 (15)	39 (85)	38 (33-43)	-		(0.3-3.4)
Two - year PFS according to PD-L1						
PD-L1 1-49%	6 (19)	26 (81)	26 (22-30)	-	0.98	0.99
PD-L1 ≥ 50%	9 (20)	37 (80)	35 (29-41)	-		(0.4-2.8)
Three - year PFS according to PD-L1						
PD-L1 1-49%	7 (22)	25 (78)	25 (20 – 29)	27 (15-27)	0.48	1.5
PD-L1 ≥ 50%	8 (17)	38 (63)	36 (30 – 42)	-		(0.5-4.2)

*Ratio upper row/lower row.

all the mentioned clinical trials, the most common immunotherapy-mediated side effect was hypothyroidism, which was the case in our study as well[18-20]. In 7 (9%) of our patients, there was a temporary or permanent interruption of pembrolizumab therapy, which is an even lower percentage than in the aforementioned clinical trials[18-20]. We can conclude that the safety profile of pembrolizumab from clinical trials fully matches the results from real clinical practice.

Comparison with Similar Research

Our data are mostly consistent with real-world data, as they are with data from clinical trials. In one retrospective study with data from a large American database, the estimated duration of treatment with pembrolizumab in the ECOG PS 0-1 patient group was 7.4 months, while in our case, it was 10.1 and 10.3 months[21]. In the aforementioned research, the median age was slightly higher than in the studies and in our research. In addition, in the same research, in the majority of patients, it was non-squamous cancer that was discovered in stage 4, and the patients were active or former smokers, which correlates with our data[21]. It is interesting to mention a study from 4 Israeli centers in which OS and PFS were slightly lower than ours and in which patients were also divided into groups according to PD-L1 expression, but OS was higher in the group of patients with PD-L1 1-49%[22]. A possible explanation for this fact, offered by the authors, is a high probability of hyperprogression during immunotherapy treatment. Correspondingly, pseudoprogression occurred at the first evaluation in as many as 18% of our patients[22]. Certain worldwide studies included patients of all ECOG statuses, for example, a retrospective analysis of data from the United States of America in which patients with PD-L1 1-49% had a median OS of 13.8 months and patients with PD-L1≥ 50% 16.5 months[23]. The above data are similar to ours but still somewhat lower, most likely due to the difference in the ECOG status of the included patients.

Conclusions

The data from our research correspond to those from clinical trials and to real-world data, but there are instances in which our results are better than those from other centers. The explanation for this fact probably lies in certain limitations of our study – a small sample of patients and the exclusion of patients who received less than 3 cycles of pembrolizumab. The demographic data on the patients also agree with the available data from studies and global research. Finally, we can conclude that pembrolizumab in monotherapy and in combination with chemotherapy in the treatment of lung cancer shows an excellent efficacy and safety profile and therefore continues to be the standard of treatment for metastatic non-small cell lung cancer. Nevertheless, there is a need for a more objective tool for assessing the patient's general condition, which, in addition to the ECOG status, would include other parameters, such as patient comorbidities.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgments

We would like to thank Vedrana Čerina, an English language professional, for her help with the proofreading.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article. Possible publication of the article will be funded by the authors themselves.

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Data Availability

The datasets analyzed during the current study are not publicly available because they were collected from the archive and the information system of University Hospital Centre Osijek but are available from the corresponding author on reasonable request.

Informed Consent

Informed consent was not obtained from participants included in the study because data was collected retrospectively from the archive and the information system of University Hospital Centre Osijek.

Ethics Approval

The research was approved by the Ethics Committee of University Hospital Centre Osijek (number of acceptance: R1-4012/2023) and was carried out in accordance with all the principles of the Declaration of Helsinki, with patient anonymity and data confidentiality maintained.

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