

## ORIGINAL ARTICLE

# First-line pembrolizumab efficacy in patients with advanced non-small cell lung cancer: A Bi-center retrospective, real-life experience study

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## Summary

**Purpose:** Immune checkpoint inhibitors (ICIs) have caused a paradigm shift in the treatment landscape of advanced non-small cell lung cancer (NSCLC). Real-world practice may be different from randomized studies. The purpose of this study was to investigate the real-world pembrolizumab efficacy with or without chemotherapy.

**Methods:** All consecutive patients aged over 18 years who were diagnosed as metastatic NSCLC and received at least one dose of first-line pembrolizumab treatment were retrospectively reviewed. The patients hadn't received no previous systemic therapy.

**Results:** A total of 44 patients treated with pembrolizumab were enrolled. Just over half (51.2%) of the patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS)  $\geq 2$ , and 36.4% had liver metastasis. There were no patients with driver mutations, 18.2% had programmed

death ligand-1 (PD-L1)  $\geq 50\%$  expression and 82.3% were treated with pembrolizumab plus chemotherapy. The median progression-free survival (PFS) and overall survival (OS) were 3.0 months (95% CI: 0.9-5.0 months) and 6.6 months (95% CI: 0.7-12.4 months), respectively. Multivariate analysis identified liver metastasis and adrenal metastasis as independent predictors of OS.

**Conclusions:** PFS, OS, objective response and disease control rate results were significantly worse than in randomized studies. ICIs are not an infallible treatment option to be used for every patient with advanced NSCLC encountered in daily clinical practice. Attention should be paid to stringent eligibility criteria used in randomized studies as much as possible and try to manage patients according to these criteria.

**Key words:** advanced NSCLC, immune checkpoint inhibitors, pembrolizumab, first-line, real-life experience

## Introduction

Lung cancer is the most common cause of cancer-related deaths worldwide. Approximately 85% of lung cancers are non-small cell lung cancers (NSCLC) [1]. The majority of patients with NSCLC are diagnosed in advanced stage. Only 30% have resectable disease at diagnosis and a considerable number of patients have recurrence after resection [2,3]. Some dramatic changes occurred in the treatment of advanced NSCLC in the last decade. For patients with NSCLC associated with driver

mutations, targeted therapies became redefined treatment options [4,5]. These therapies are ineffective in those whose tumors lack such genetic alterations, who comprise the majority of patients NSCLC, and immune checkpoint inhibitors (ICIs) have become integrated into the treatment of such patients [6-11]. In patients with advanced NSCLC whose tumors have programmed death ligand-1 (PD-L1) expression  $\geq 50\%$  not harboring genomic alterations, treatment with single-agent pembroli-

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zumab, humanized immunoglobulin (Ig)-G4 monoclonal antibody to the programmed cell death 1 (PD-1) receptor, were associated with better progression-free survival (PFS) and overall survival (OS) than platinum-doublet chemotherapy [8]. For non-squamous, EGFR-ALK wild-type PD-L1 unselected NSCLC, pembrolizumab plus platinum agent and pemetrexed has improved PFS and OS relative to platinum plus pemetrexed [9]. The addition of pembrolizumab to carboplatin plus paclitaxel or nab-paclitaxel improved PFS and OS in patients with PD-L1 unselected advanced squamous NSCLC [10]. Single-agent pembrolizumab had similar OS relative to platinum-based doublet chemotherapy in patients with PD-L1 expression between 1% and 49% [11]. According to the results of these trials, single-agent pembrolizumab is the preferred treatment option for patients with advanced NSCLC and a PD-L1 tumor proportion score (TPS) of 50% or higher. For patients with negative (TPS 0%) and low positive (TPS 1-49%) PD-L1 expression, pembrolizumab plus chemotherapy combinations are the standard of care. Single-agent pembrolizumab is a treatment option for patients with PD-L1 expression between 1% and 49%, who are ineligible or decline combination of doublet platinum with or without pembrolizumab [12]. These treatment options revolutionized advanced NSCLC treatment and have led to improvements in survival and quality of life.

Real-world practice may be different from randomized studies. The eligibility criteria of clinical trials have become increasingly stringent and only selected patients can participate in most trials. Therefore, clinical trials may not be entirely representative on daily clinical practice.

The aim of this study was to investigate the real-world pembrolizumab efficacy with or without chemotherapy. We also sought the role of clinico-pathologic prognostic and predictive factors with first-line pembrolizumab treatment in patients with advanced NSCLC.

## Methods

All consecutive patients aged over 18 years who were diagnosed as having metastatic NSCLC and received at least one dose of first-line pembrolizumab treatment at Dr. Burhan Nalbantoglu State Hospital (Nicosia, Cyprus) and Near East University Hospital (Nicosia, Cyprus) between March 2018 and December 2020 were retrospectively reviewed from patient files, the center's databases, and chemotherapy ward files. The patients received no previous systemic therapy. Patients with a history of autoimmune disease or another malignancy were not excluded from the study. Ethical approval was obtained from the individual institution-

al ethical review committees and consent waiver was granted in view of the retrospective nature of evaluation. All procedures in the study which involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and also in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Pembrolizumab was administered at 200 mg q 21 days with or without chemotherapy. For squamous cell carcinoma (SQ), 4-6 cycles carboplatin (at a dose calculated to produce an area under the concentration-time curve (AUC) of 5 mg per milliliter per min) on day 1 plus paclitaxel (175-200

**Table 1.** Baseline patient and tumor characteristics

Characteristics	n (%)
Age at start (years)	
Median	66
Range	47-86
Sex	
Male	37 (84.1)
Female	7 (15.9)
Histology	
Adenocarcinoma	30 (68.2)
Squamous cell carcinoma	12 (27.2)
Adenosquamous	1 (2.3)
NSCLC, NOS	1 (2.3)
PD-L1	
Negative	22 (50.0)
1-49%	7 (15.9)
≥50%	8 (18.2)
Unknown	7 (15.9)
ECOG performance status score no (%)	
0-1	21 (48.8)
2-4	23 (51.2)
Smoking status	
Current or former smoker	42 (95.5)
Never smoked	2 (4.5)
CNS metastasis	
Yes	4 (9.1)
No	40 (90.9)
Liver metastasis	
Yes	16 (36.4)
No	28 (63.6)
Bone metastasis	
Yes	16 (36.4)
No	28 (63.6)
Malignant pleural effusion	
Yes	10 (22.7)
No	34 (77.3)
Adrenal gland metastasis	
Yes	12 (27.3)
No	32 (72.7)

mg per m<sup>2</sup> of body surface area) on day 1 q 21 days was administered. Carboplatin (AUC area 5 mg per milliliter per min) plus pemetrexed (500 mg per m<sup>2</sup>), was administered intravenously every 3 weeks for non-squamous (non-SQ) patients.

Patient demographics: Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the time of initiating pembrolizumab with or without chemotherapy; smoking history; histology; molecular profiling for EGFR, ALK, ROS 1, and BRAF when available; PD-L1 status (DAKO; Carpinteria, CA, USA) when available; sites of metastatic spread at the time of initiating pembrolizumab with or without chemotherapy; post-progression treatments; number of pembrolizumab doses; response status, date of death or last follow-up; and immune-related adverse events (irAEs) were recorded. The response assessment was performed mostly with computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG PET)-CT every 3 months. Best radiographic response, i.e. complete remission (CR), progressive disease (PD), partial response (PR), and stable disease (SD), and the time to achieve the best response was recorded using response evaluation criteria in solid tumors (RECIST) criteria V 1.1 [13]. CR was defined as radiographic disappearance of all target lesions, PR was defined as a 30% decrease in target lesions, SD was defined as no significant increase or decrease in the size of the target lesions, and PD was defined as the appearance of the new lesions or an increase in the size of the known lesions (20% or more). The immune-related adverse events (irAEs) were determined, characterized, and graded by two investigators (O.D. and P.O.) according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTACE), version 4.0.

### Statistics

Demographic characteristics were described using frequencies and percentages for categorical variables and medians and ranges for continuous variables. The OS was defined as the number of months between the first pembrolizumab treatment and death or censored at the date of the last patient follow-up. The objective response rate (ORR) was calculated as the percentage of patients achieving PR and CR among all treated patients. The disease control rate (DCR) was defined as the percentage of patients achieving CR, PR and SD. The PFS was defined as the number of months between the first pembrolizumab treatment and death or progression, whichever occurred first (censored at the date of the last patient contact). The OS and PFS curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using a logistic regression model. A Cox proportional hazards model was used to identify independent predictive and prognostic factors. The multivariate models were fitted with the inclusion of the covariates that resulted in statistically significant difference in the univariate model.  $P < 0.05$  was considered statistically significant in all analyses. Analyses were conducted using the SPSS version 22 software (IBM Corp. Chicago, IL).

## Results

### Patients

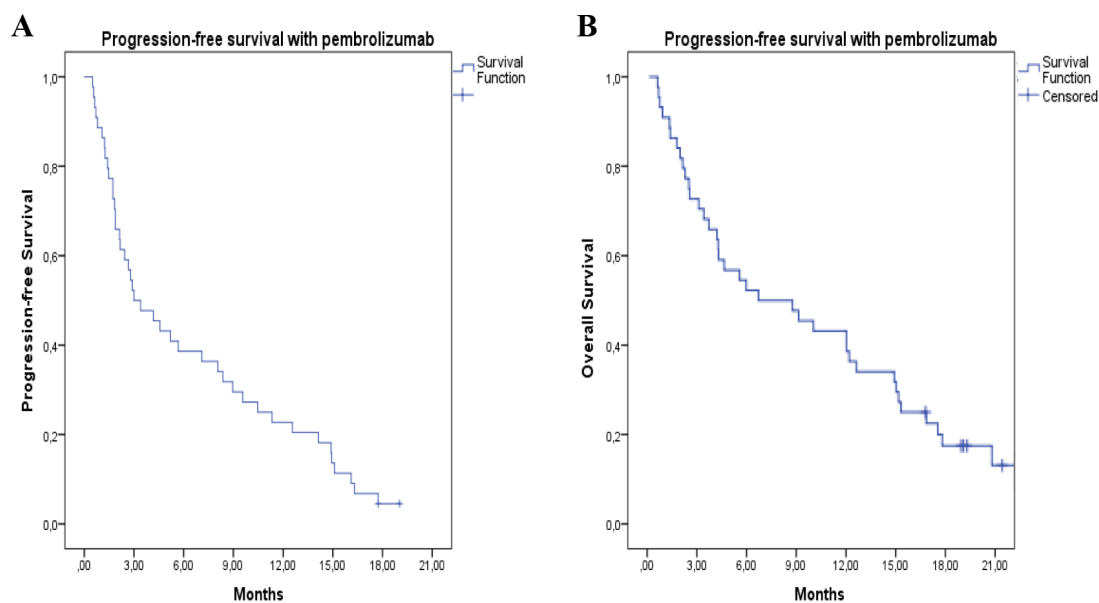
A total of 44 patients treated with pembrolizumab were enrolled. The median duration of follow-up (defined as the time from initiation of pembrolizumab treatment to death or the date of

**Table 2.** Treatment characteristics according to histological subtype and PD-L1 status

	Pembrolizumab plus carboplatin-pemetrexed (n=23) n (%)	Pembrolizumab plus carboplatin-paclitaxel (n=12) n (%)	Single agent pembrolizumab (n=9) n (%)
Squamous cell carcinoma	-	10 (22.7)	2 (4.5)
PD-L1 status			
negative	-	6 (13.6)	1 (2.3)
1-49%	-	2 (4.5)	-
≥50%	-	2 (4.5)	1 (2.3)
Unknown	-	-	-
Non-squamous cell carcinoma	23 (52.3)	2 (4.5)	7 (15.9)
PD-L1 status			
negative	14 (31.8)	-	1 (2.3)
1-49%	3 (6.8)	2 (4.5)	-
≥50%	1 (2.3)	-	4 (9.0)
Unknown	5 (11.4)	-	2 (4.5)
Initiation of treatment			
Outpatient setting	14 (31.8)	9 (20.5)	3 (6.8)
Hospitalized setting	9 (20.5)	3 (6.8)	6 (13.6)
Post-progression treatment	9 (20.5)	6 (13.6)	4 (9.0)

the last follow-up visit) was 7.6 months (range, 0.5 to 24.5) and only one patient was still receiving pembrolizumab. The baseline clinical and tumor characteristics at the initiation of pembrolizumab are presented in Table 1. Of note, the median age was 66 years (range, 47-86). The majority of patients were male (n=37, 84.1%) and

ex-smokers or current smokers (n=42, 95.5%). Just over half (51.2%) of the patients had an ECOG PS  $\geq 2$ , 27.2% of patients were affected by squamous cell carcinoma (SQ) and 36.4% had liver metastasis. There were no patients with driver mutations and 18.2% of patients had PD-L1  $\geq 50\%$  expression.



**Figure 1.** Kaplan-Meier curves of (A) progression-free survival (PFS) and (B) overall survival (OS) in the global population.

**Table 3.** Univariate and multivariate analyses of overall survival (OS) and progression free survival (PFS)

Variables	Progression-free survival (PFS)		Overall survival (OS)	
	Unadjusted HR (95% CI), p value	Adjusted HR (95% CI), p value	Unadjusted HR (95% CI), p value	Adjusted HR (95% CI), p value
ECOG PS $\geq 2$	2.14 (1.14-4.00), 0.017	1.59 (0.71-3.57), 0.257	1.82 (0.95-3.49), 0.068	-
Histology-Non-SQ	1.10 (0.56-2.15), 0.783	-	1.05 (0.51-2.12), 0.891	-
Age at start (years)		-		-
<65 vs $\geq 65$	0.86 (0.46-1.61), 0.656		0.92 (0.48-1.78), 0.826	
PD-L1	N/A, .006	N/A, .036	N/A, .264	-
Negative	1	1	1	
1-49%	0.16 (0.05-0.53) 0.003	0.20 (0.05-0.72) 0.014	0.43 (0.16-1.19) 0.107	
$\geq 50\%$	0.37 (0.15-0.92) 0.033	0.44 (0.17-1.13) 0.092	0.74 (0.32-1.72) 0.488	
Presence of bone metastasis	3.89 (1.83-8.26), <0.001	2.94 (1.05-8.21), 0.039	2.08 (1.06-4.07), 0.033	1.50 (0.73-3.06), 0.261
Presence of adrenal gland metastasis	2.00 (1.00-4.00), 0.048	0.84 (0.31-2.31), 0.746	2.69 (1.31-5.48), 0.006	2.58 (1.20-5.52), 0.014
Presence of malignant pleural effusion	2.09 (0.98-4.46), 0.056	-	0.97 (0.44-2.14), 0.950	-
Presence of liver metastasis	1.69 (0.88-3.25), 0.112	-	2.18 (1.10-4.32), 0.025	2.13 (1.05-4.34), 0.036
irAEs	0.64 (0.26-1.56), 0.334	-	0.77 (0.32-1.85), 0.561	-

### Treatment

The median number of treatment cycles for pembrolizumab was 3 (range, 1 to 18) and 15.9% of patients received only one cycle of pembrolizumab before death. The majority of patients were treated with pembrolizumab plus chemotherapy (n=35, 82.3%) and 40.9% were initiated treatment in hospitalised setting. Treatment characteristics according to the histologic subtype and PD-L1 status are shown in Table 2.

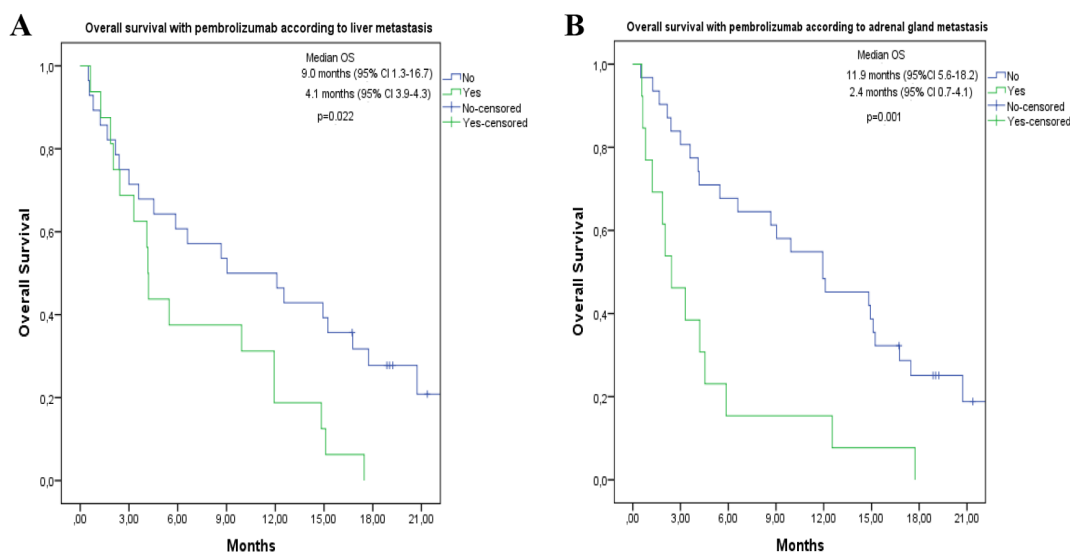
### Efficacy

Overall, 38 patients died by the time of the last follow-up (19/12/2020). The median PFS and

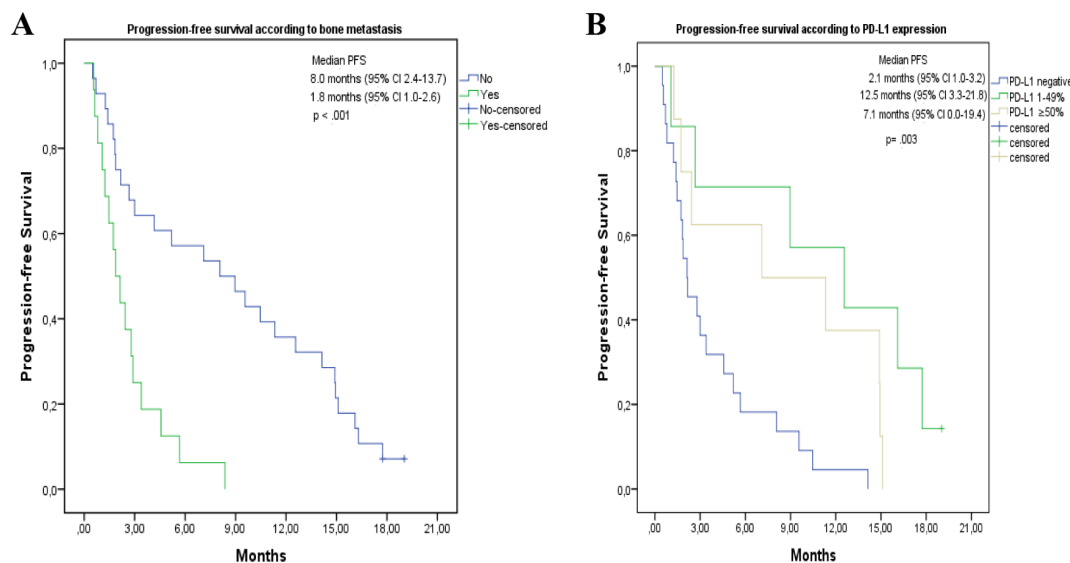
OS were 3.0 months (95% CI: 0.9-5.0 months) (Figure 1A) and 6.6 months (95% CI: 0.7-12.4 months) (Figure 1B), respectively. Nineteen (43.1%) of the patients received second-line treatment after progression.

### Prognostic and predictive factors

We evaluated the prognostic and predictive role of ECOG PS, histologic subtype, age at initiation of pembrolizumab, PD-L1, site of metastatic location, and irAEs. The univariate analysis revealed that liver, adrenal gland, and bone metastasis were significantly associated with shortened OS. In multivariate analysis, liver and adrenal gland metas-



**Figure 2.** Kaplan-Meier plot for (A) the overall survival (OS) stratified by liver metastasis and (B) adrenal gland metastasis (95% CI, 95% confidence interval).



**Figure 3.** Kaplan-Meier plot for (A) the progression-free survival (PFS) stratified by bone metastasis and (B) PD-L1 expression (95% CI, 95% confidence interval).

tasis were confirmed as being independently associated with inferior OS (Table 3). The median OS was shorter in patients with liver metastasis than in those without metastasis (4.1 vs. 9.0 months, log-rank  $p=0.022$ ) (Figure 2A). The median OS was also shorter in patients with adrenal gland metastasis than in those without metastasis (2.4 vs. 11.9 months, log-rank  $p=0.005$ ) (Figure 2B).

Adrenal gland and bone metastasis, negative PD-L1 expression, and ECOG PS  $\geq 2$  were associated with worse PFS in the univariate analysis. In the final multivariate model, negative PD-L1 status and bone metastasis remained independently associated with inferior PFS. Patients without bone metastasis had better median PFS than those with metastasis (8.0 vs. 1.6 months, log-rank  $p<0.001$ ) (Figure 3A). As shown by representative Kaplan-Meier survival curves (Figure 3B), patients whose PD-L1 was negative had significantly poorer PFS outcomes.

In the entire study population, the ORR and DCR was 36.4% and 59.1%, respectively. Table 4 summarizes the univariate and multivariate analyses of ORR and DCR. ECOG PS  $\geq 2$  ( $p=0.039$ ), surrenal ( $p=0.039$ ) and bone metastasis ( $p=0.010$ ) were associated with a lower likelihood of response in the univariate analysis. The PD-L1 expression of 1-49% ( $p=0.011$ ) and presence of irAEs were associated with superior ORR ( $p=0.030$ ). The final logistic regression model confirmed that bone metastasis

( $p=0.035$ ) was independently associated with a lower response rate, and PD-L1 1-49% was associated with a higher likelihood of response ( $p=0.027$ ).

For ECOG PS  $\geq 2$ , the presence of bone and adrenal gland metastasis was associated with a lower disease control rate. The PD-L1 positivity ( $p=0.029$ ), and the presence of irAEs was associated with a higher likelihood of disease control ( $p=0.049$ ). In multivariate analysis, bone metastasis was confirmed to be independent predictor of a worse DCR ( $p=0.020$ ).

### Discussion

In our study cohort, PFS, OS, ORR, and DCR results were significantly worse than in randomized studies [8-10]. Several real-life experience studies also showed worse PFS and OS data than in the experimental arms of randomized trials [14-18]. Randomized studies with ICIs had strict eligibility criteria, such as patients who had an ECOG PS 0-1, adequate organ function, no history of prior malignancy, and no active CNS metastasis. It is difficult to apply these criteria in everyday clinical practice. In our study cohort, 51.2% of patients had ECOG PS  $\geq 2$ . In retrospective real-life experience studies, poor PS was associated with inferior rates of PFS, OS, and a lower likelihood of response [17,18]. In univariate analysis, we found that ECOG PS 2 or higher was associated with poor PFS and a lower

**Table 4.** Univariate and multivariate analyses of objective response and disease control

Variables	Objective response		Disease control	
	Unadjusted OR (95% CI), <i>p</i> value	Adjusted HR (95% CI), <i>p</i> value	Unadjusted OR (95% CI), <i>p</i> value	Adjusted HR (95% CI), <i>p</i> value
ECOG PS $\geq 2$	0.25 (0.06-0.93), 0.039	0.91 (0.11-7.24), 0.936	0.17 (0.04-0.64), 0.009	0.24 (0.02-2.81), 0.126
Histology-Non-SQ	0.73 (0.18-2.85), 0.655	-	0.60 (0.15-2.28), 0.455	-
Age at start (years)				
<65 vs $\geq 65$	0.71 (0.20-2.50), 0.599	-	0.66 (0.19-2.26), 0.511	-
PD-L1	N/A, .027	N/A, .086	N/A, .029	N/A, .143
Negative	1	1	1	1
1-49%	14.16 (1.82-109.85) 0.011	11.92 (1.31-107.91) 0.027	10.00 (1.39-71.86) 0.022	7.16 (0.80-63.74) 0.077
$\geq 50\%$	5.66 (0.89-36.08) 0.066	2.66 (0.31-22.88) 0.371	6.66 (1.09-40.43) 0.039	4.30 (0.52-35.56) 0.175
Presence of bone metastasis	0.05 (0.00-0.49), 0.010	0.06 (0.00-0.83), 0.035	0.04 (0.00-0.37), 0.004	0.05 (0.00-0.62), 0.020
Presence of adrenal gland metastasis	0.10 (0.01-0.89), 0.039	0.30 (0.02-4.01), 0.363	0.08 (0.00-0.69), 0.022	0.24 (0.02-2.81), 0.258
Presence of malignant pleural effusion	0.35 (0.06-1.94), 0.233	-	0.54 (0.12-2.46), 0.429	-
Presence of liver metastasis	0.70 (0.19-2.58), 0.595	-	0.52 (0.14-1.90), 0.328	-
irAEs	12.27 (1.28-117.44), 0.030	7.18 (0.50-102.95), 0.146	9.61 (1.01-91.15), 0.049	5.48 (0.34-86.21), 0.226

likelihood response or disease control. However, multivariate analysis revealed that ECOG PS had no independent association with PFS, OS, ORR or DCR. Therefore, we thought that poor PS was an indicator of higher disease burden and aggressive tumor biology rather than an independent prognostic or predictive variable. In our study cohort, 15.9% of patients received only one cycle of pembrolizumab. Eighteen (40.9%) of the patients were given pembrolizumab in hospitalised setting. Nine of 44 patients had synchronous-metachronous cancer.

In our study cohort, 43.1% of the patients who progressed received second-line treatment. Some studies reported that more patients received second-line treatment after progression with first-line pembrolizumab treatment [19,20]. Therefore we think that our study cohort consisted of individuals who had more aggressive cancers and died earlier. All treatment protocols are reimbursed by the state in our country. The majority of patients and their relatives have an absolute treatment expectation and concepts such as best supportive care or hospice care do not exist legally. Perhaps some of the patients were only candidates for best supportive care in our study. However, our survival outcomes were worse than in the chemotherapy era [21,22]. We would expect more positive outcomes with the addition of pembrolizumab, even though poor candidate selections were made. Our centers were located in Cyprus, which is a small island country. We planned a study to investigate possible founder mutations that could explain our poor outcomes in patients with NSCLC.

Nowadays, the efficacy of ICIs according to different metastatic sites is being extensively investigated. Tumor microenvironments differ across various organ sites and it may affect the activity of ICIs [23,24]. Bone and bone marrow are immune regulatory organs. Therefore, ICI and chemotherapy responses may be affected by bone metastasis [25,26]. The presence of bone metastasis was significantly associated with poor PFS, lower likelihood of response and disease control in our study. None of the randomized studies with ICIs specifically stratified patients according to the presence of bone metastases. Some retrospective studies investigated the impact of bone metastasis on the efficacy of ICI treatment. In a nivolumab expanded access program, bone metastasis was associated with a lower likelihood of response and poorer PFS and OS [27]. In another retrospective study, organ-specific responses with nivolumab in patients with advanced NSCLC were investigated. Nine of 12 patients with bone metastases had progressive disease [23]. Our study results are com-

patible with these studies. A study that investigated the role of bone metastases on two different advanced NSCLC cohorts, ICI monotherapy, and an ICI combination with chemotherapy, bone metastasis was found to be associated with poor PFS and OS in the ICI alone cohort but not in the combination cohort. The authors hypothesized that chemotherapy could overcome the adverse effect of bone metastasis [28]. In our study, we treated 82.3% of patients with chemotherapy plus pembrolizumab. This result shows that bone metastasis is associated with poor PFS, OS, and a lower likelihood of response in patients treated with ICI alone or ICI combined with chemotherapy.

We found that the presence of liver metastasis was significantly and independently associated with poor OS. The presence of liver metastasis was associated with poor prognosis in the chemotherapy era. The median cancer-specific survival was 6.2 months for patients with liver metastases in a SEER database analysis [29]. Liver metastasis was associated with lower CD8<sup>+</sup> T cell counts at the invasive margin of tumors [30,31]. Therefore, there were some doubts about the efficacy of ICIs in patients with liver metastasis. HRs for OS with ICIs versus a control arm were similar among patients with and without liver metastases. However, absolute survival was poor in patients with liver metastasis [18,32-34]. Our study results are compatible with the literature. Adrenal gland metastasis was independently associated with poor OS in our study. Except for solitary adrenal metastasis, data about the prognostic value of adrenal gland metastasis are scarce [35]. More studies are needed to confirm this finding and reveal the underlying mechanism.

The PD-L1 levels were significantly associated with PFS and objective responses. We found that PD-L1 1-49% NSCLC patients were associated with better PFS and objective response rates than PD-L1 negative patients. These were expected outcomes and compatible with the literature [11,36,37]. PD-L1 expression has been approved as a companion diagnostic test for first-line pembrolizumab treatment [8,37]. No statistically significant difference between the PD-L1 negative and PD-L1 50% or higher group was found. We had a low number of patients in the 50% or higher group and this may explain the non-significant outcomes in this group. PD-L1 analyses of 7 of 44 patients were not available and this may have affected the statistical analysis outcomes.

Our study has several limitations. The retrospective design and relatively small sample size limited the significance of the subgroup analysis. PD-L1 analyses were not available in 15.9% of

patients and this may have affected the statistical analysis. In conclusion, ICIs changed the landscape of treatment for advanced NSCLC. We always want to do the best we can for our patients as medical oncologists. However, our study results revealed that ICIs are not an infallible treatment option to be used for every patient with advanced NSCLC encountered in daily clinical practice. We

should pay attention to stringest eligibility criteria used in randomized studies as much as possible and try to manage patients according to these criteria.

### Conflict of interests

The authors declare no conflict of interests.

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