Original Article

Real-Life Analysis of Immunotherapy as the Second or Later Lines Treatment in Patients with Metastatic Non-Small Cell Lung Cancer

Metastatik Küçük Hücre Dışı Akciğer Kanseri Hastalarının İkinci veya İleri Sıra Tedavisinde İmmünoterapinin Gerçek Yaşam Analizi

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ABSTRACT

Background: Immunotherapy agents such as atezolizumab and nivolumab are appropriate option for non-small cell lung cancer (NSCLC) accounts in the absence of driver mutation, regardless of PDL-1 expression in second and later line setting. Herein we aimed to evaluate the efficacy and safety of immunotherapy for the second and later line settings in metastatic NSCLC patients as a single center experience.

Methods: Totally, 37 patients with metastatic NSCLC who received atezolizumab or nivolumab in the second or later lines were included. Clinicopathological features of patients and survival outcomes were analyzed. The safety profile and the factors that may predict survival were also evaluated.

Results: Twenty-nine (78.4%) of patients were men and 8 of patients (21.6%) were woman with median age of 61 years (range:42-80). Atezolizumab was preferred in 22 (59.5%) of these patients and nivolumab in 15 (40.5%) of them. Objective response rate was 35.1%. At a median follow up of 22.5 months, median progression-free survival (PFS) was 4.7 months, median overall survival (OS) was 24.1 months. Univariate analysis for PFS revealed that gender (p=0.03), age (p=0.005), the presence of brain metastasis (p=0.02), PDL-1 status >1% (p=0.035), ECOG PS (p=0.04) and the good response to frontline treatment (p=0.015) were found to be significant prognostic indicators. It also showed that the presence of brain metastasis (p=0.03), PDL-1 status >1% (p=0.027), good response to frontline treatment (p=0.022) and atezolizumab preference (p=0.018) were prognostic factors for OS.

Conclusion: Our real-life analysis indicated that atezolizumab and nivolumab improved survivals with good safety profile in second and later lines treatment of metastatic NSCLC patients.

Keywords: Non small cell lung cancer, atezolizumab, nivolumab, second or later line treatment

ÖZET

Amaç: Atezolizumab ve nivolumab, driver mutasyon yokluğunda, küçük hücre dışı akciğer kanserinin (KHDAK) ikinci ve sonraki basamak tedavisinde PDL-1 durumundan bağımsız olarak kullanılabilen iyi bir seçenektir. Burada, metastatik KHDAK'li hastalarda ikinci ve sonraki sıra tedavide immünoterapinin etkinliğini ve güvenliğini değerlendirmeyi tek Merkez deneyimi olarak amaçladık.

Gereç ve yöntem: Çalışmaya, ikinci veya sonraki sıralarda atezolizumab veya nivolumab alan toplam 37 metastatik KHDAK hastası dahil edildi. Hastaların klinikopatolojik özellikleri ve sağkalım sonuçları analiz edildi. Güvenlik profili ve sağkalımı öngörebilecek faktörler değerlendirildi.

Bulgular: Hastaların 29'u (%78.4) erkek, 8'i (% 21.6) kadın, ortanca yaş 61 (aralık: 42-80) idi. Bu hastaların 22'sinde (%59.5) atezolizumab, 15'inde (% 40.5) nivolumab tercih edilmişdi. Objektif yanıt oranı %35.1 idi. Medyan 22.5 aylık takipte, medyan progresyonsuz sağkalım 4.7 (PSK) ay iken, medyan genel sağkalım (OS) 24.1 ay olarak bulundu. PFS için tek değişkenli analizde, cinsiyet (p=0.03), yaş (p=0.005), beyin metastazı varlığı (p=0.02), PDL-1 durumu >%1 (p=0.035), ECOG PS (p=0.04) ve ilk sıra tedaviye iyi yanıt varlığı (p=0.015) anlamlı prognostik göstergeler olarak bulundu. OS için ise, beyin metastazı varlığı (p=0.03), PDL-1 durumu >%1 (p=0.027), ilk sıra tedaviye iyi yanıt varlığı (p=0.022) ve atezolizumab tercihi (p=0.018) prognostik faktörler olarak bulundu.

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Sonuçlar: Gerçek hayat analizimiz, atezolizumab ve nivolumabın, metastatik KHDAK hastalarının ikinci ve sonraki basamak tedavilerinde iyi güvenlik profili ile sağkalımı iyileştirdiğini gösterdi.

Anahtar Kelimeler: Küçük hücre dışı akciğer kanseri, nivolumab, atezolizumab, ikinci ve sonraki sıra tedavi

Introduction

Lung cancer is the mostly diagnosed cancer worldwide and causes deaths approximately 1.7 million per year [1]. Non small cell lung cancer (NSCLC) is about 80 per cent of lung cancers. Half of patients are diagnosed in the advanced setting, however survival rates are improving in recently years due to new treatment modalities [2]. Targeted therapies are appropriate option with presence of driver mutation e.g., epidermal growth factor receptor [EGFR]-mutant, anaplastic lymphoma kinase [ALK]-rearranged NSCLC. Nevertheless, in those with the lack of driver mutation immune check point inhibitors with or without chemotherapy is the best treatment option which has led to improvements in survival and quality of life [3]. Although immunotherapy is preferred at initial treatment setting, many patients are treated with frontline chemotherapy. For such patients regardless of PDL-1 expression status, anti-programmed cell death protein 1 (PD-1) or anti-programmed cell death ligand 1 (PDL-1) antibody is an appropriate option rather than single agent chemotherapy. Unlike atezolizumab and nivolumab, pembrolizumab is an option if the tumor PDL-1 has been identified on at least 1 percent of tumor cells [4-6]

Nivolumab, with the dose regimen 240 mg IV every two weeks, is an option for advanced NSCLC who progressed after platinum-based chemotherapy. In the phase III CheckMate 017 trial nivolumab compared with chemotherapy in squamous NSCLC and nivolumab improved overall survival (OS) with median 9.2 versus 6.0 months. PDL-1 status did not change the survival rates [7-9]. In the phase III CheckMate 057 trial, nivolumab versus docetaxel experienced in advanced non squamous NSCLC, nivolumab also prolonged OS with median 12.2 versus 9,4 months. However, survival improvement was seen in PDL-1 positive tumors, it was similar between nivolumab and docetaxel for those with PDL-1-negative tumors [10,11].

Atezolizumab is approved for dose schedule 1200 mg IV every three weeks. In phase III OAK trial atezolizumab compared with docetaxel in advanced pretreated NSCLC with any PDL-1 and histologic status. Atezolizumab experienced improved OS, 13.8 versus 9.6 months regardless of histology. Atezolizumab versus docetaxel did not improve the PFS or response rates. Also higher PDL-1 status was related with greater OS results [12,13].

Pembrolizumab with approved dose of 200 mg every three weeks, was associated with better survival outcomes in pretreated advanced NSCLC whom at least 1 percent tumor cell PDL-1 expression. In Keynote 010 trial compared with chemotherapy OS difference was greater in patients with PDL-1 status >50% who received pembrolizumab, median 8.2 versus 16.9 months [14,15].

Despite clinical benefits, immuno-therapies can cause uniq side effects which is called immune-related adverse events. These side effect include dermatologic, gastro-intestinal, hepatic, endocrine, and other less common inflammatory events. Rarely fulminant and even fatal toxicities may occur with immune checkpoint inhibitors. In general, treatment of moderate or severe irAEs requires interruption of the checkpoint inhibitor and the use of glucocorticoid immunosuppression. Treatment of side effects

are based on the severity of the observed toxicity. Also the toxicity grade is important for the managment of side effects [16].

In the current study, we aimed to present the contribution and reliability of the use of immunotherapy to the survival of NSCLC patients who had received at least one frontline treatment, as a single center experience.

Methods:

Between 2015 and 2021, totally 37 patients with metastatic pretreated NSCLC who have received immunotherapy were included in this study. Patients who could not complete their treatment due to financial and non-illness reasons and those who died for reasons other than cancer, and the patients with ECOG PS 3 and 4 were excluded from data analysis. Patients' data were retrospectively obtained from patients charts with respect to age, number of metastatic sites, treatment choice, duration of treatment, PDL-1 status, survival outcomes and toxicities. The Local Ethics Committee of Istanbul Medipol University approved the study on June 2021 with E-10840098-772-02-2508 decision number.

PDL-1 Expression Assessment: The PDL-1 values of the patients were evaluated with the SP142 method in patients receiving atezolizumab and with the 22C3 method in patients receiving nivolumab.

Previous Treatment: As first-line therapy, 13 of 17 patients with adenocarcinoma histology received a paclitaxel-platinum regimen, while 4 received a pemetrexed-platinum regimen. Of 8 patients with squamous histology, 6 received paclitaxel-platinum and 2 received gemcitabine-platin chemotherapy regimen. Twelve patients using immunotherapy in the third-line received platinum-based doublet chemotherapy in the frontline setting, while they received gemcitabine-docetaxel chemo-therapy regimen in the second-line treatment.

Statistical analysis:

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Survival analysis and curves were established according to the Kaplan-Meier method and compared by the long-rank test. PFS was defined as the time from diagnosis to the last follow-up and the time until relapse as being the time from diagnosis to the first evidence of relapse. In addition, OS was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analysis of prognostic factors related to survival were performed by the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than or equal to 0.05 were accepted to be statistically significant.

Results:

Twenty-nine (78.4%) of patients were men and 8 of patients (21.6%) were woman with median age of 61 years (range:42-80). At the initial diagnosis, the majority of patients (64.9%) had advanced stage. Brain metastasis were detected in 15 patients (40.5%) at the initial diagnosis or during treatment. Histopathologically, most patients had adenocarcinoma (n=23, 62.2%). Eight of patients had type 2 diabetes mellitus, ten of patients had hypertension, in addition seven of patients had chronic obstructive lung disease. Patients and tumor characteristics are shown in Table 1.

PDL-1 positivity in adenocarcinoma histology was 52.2%, response rate to immunotherapy was 91.3%, while PDL-1 positivity in squamous cell histological subtype was 71.4% and response rate to immunotherapy was 85.7%. PDL-1 expression status was classified

Table 1. Patient and tumor characteristics

Characteristics	n	%
Total patients	37	
Age,years		
Median, range	61 (42-80)	
Gender		
Male	8	21.6
Female	29	78.4
Histopathological type		
Adenocarcinoma	23	62.2
Squamous cell carcinoma	13	35.1
Others	1	2.7
Initial clinical TNM stage		
Stage III	13	35.1
Stage IV	24	64.9
ECOG PS		
0	15	40.5
1	8	48.6
2	4	10.8
Tumor PD-L1 expression		
< 1%	21	63.6
1-49 %	8	24.2
>50%	4	12.1
Oncodriver mutation		
Absent	34	91.9
Present	3	8.1
Previous chemotherapy		
1	25	67.6
≥2	12	32.2
Choice of immunotherapy agent		
Nivolumab	15	40.5
Atezolizumab	22	59.5

Table 2: Response rates according to the RECIST 1.1

Response rate	n (%)
Complete response	0
Partial response	13 (35.1)
Stable disease	21 (56.8)
Progressive disease	16 (8.1)
Objective response rate (CR+PR)	13 (35.1)

*CR: Complete response, PR: Partial response,

as <1% in 21 (63.6%), 1-49% in 8 (24.2%) and >50% in 4 (12.1%) patients. There were three patients with presence of driver mutation as EGFR mutation who had adenocarcinoma histology. Therefore, they received targeted therapy in front-line setting. While 25 (67.6%) patients received immunotherapy in the second line setting, 12 patients (32.2%) received in the third and subsequent lines. Atezolizumab was preferred in 22 (59.5%) of these patients and nivolumab in 15 (40.5%) of them. The median cycles and duration of treatment were 5 (range: 2-24) and 3.7 months (range: 1.7-29.6).

Of the 22 patients who were treated with atezolizumab, 5 (20.8%) had partial response (PR) and 14 (58.3) had stable disease (SD). The PDL-1 expression level was measured in 22 of these patients, and the status >1% was measured in 10 of patients (54.2%). Twelve (50%) of the 22 patients used atezolizumab as a second line therapy.

Of the 15 patients who received nivolumab, 8 (53.3%) had PR and 7 (46.7%) had SD. The PDL-1 status was measured in 13 (86.7%) of these patients, and the PDL-1 status was >1% in six patients. Thirteen (86.7%) of 15 patients used nivolumab in second line setting.

Objective response rate (ORR) was 35.1% (Table 2). At a median follow up of 22.5 months, median PFS time was 4.7 months, while median OS time was 24.1 months (Figure1, Figure2). Brain metastasis occurred in 15 patients ongoing or pretreatment which were treated with radiotherapy. Cranial metastasis progressed only in 3 patients after radiotherapy. Pseudo progression was seen in four patients (10.8%), hyper progression did not occur in any patients.

Univariate analysis for PFS revealed that gender (p=0.03), age (p=0.005), the presence of brain metastasis (p=0.02), PDL-1 status >1% (p=0.035), ECOG PS (p=0.04) and the good response to frontline treatment (p=0.015) were found to be significant prognostic indicators. It also showed that the presence of brain metastasis (p=0.03), PDL-1 status >1% (p=0.027), good response to frontline treatment (p=0.022) and atezo-lizumab preference (p=0.018) were prognostic

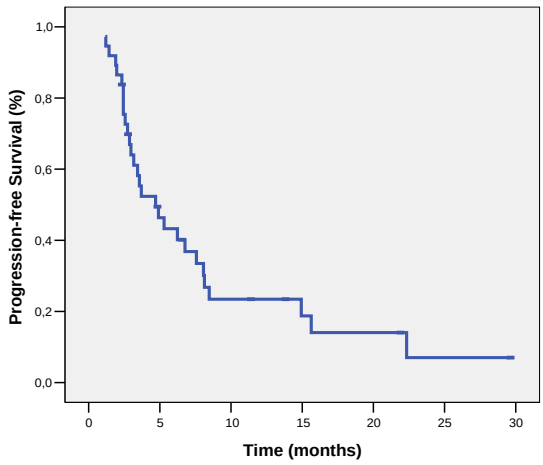

Figure 1: Median progression-free survival curve in patients with metastatic NSCLC

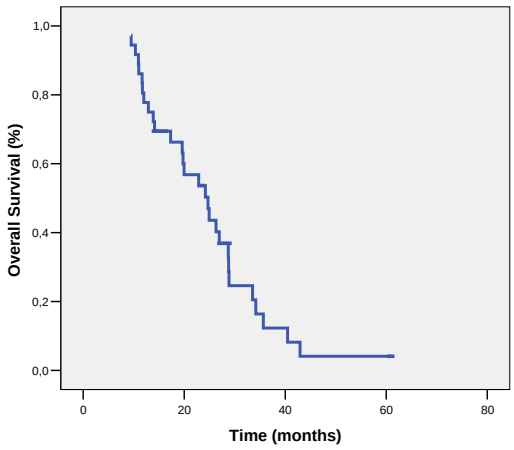

Figure 2: Overall survival curve in patients with metastatic NSCLC

factors for OS (Figure 3, Figure 4). Multivariate analysis indicated that good response to immunotherapy (HR:5.02, p=0.038) and good response to front line treatment (HR: 0.48, p=0.13), atezolizumab preference (HR:3.23, p=0.034) were significantly independent prognostic factors for OS. Figure 5 shows the OS time which was significantly better for patients treated with atezolizumab compared with nivolumab arm. Moreover, gender (HR: 5.18, p = 0.0018), age (HR: 0.18, p = 0.003), ECOG PS (HR: 11.3, p =0.002), PDL status >1% (HR:0.32, p= 0.006) and good response to immunotherapy (HR: 0.26, p=0.002) were found to be significant independent prognostic indicators for PFS by multivariate analysis. Table 3 shows multivariate analysis for overall survival and progression-free survival.

The most common grade 3/4 adverse events regarding immunotherapy were pneumonitis in 3 patients (8.1%), colitis in 1 patient (2.7%). There was no need to discontinue the treatment due to side effects in neither nivolumab nor atezolizumab. While the dose was delayed in five (33%) of the nivolumab patients due to side effects, the dose was delayed in four (16.7%) of the atezolizumab patients. Moreover, rash (18.2%) and hypothyroidism (24.3%) were common immune-related grade 1-2 adverse events.

Discussion:

Initial treatment approach of advanced NSCLC patients is treating with immunotherapy in combination with platinum-based doublet chemotherapy in front line setting [17]. However, many patients will have treated with only platinum-based doublet chemotherapy. For such patients in the second line setting incorporation of immunotherapy is the preferred approach [3,12,14]. Nivolumab or atezolizumab are appropriate options regardless of tumor PDL-1 expression [4,5]. Pembrolizumab is an option for the tumors with at least >1% of PDL-1 status [6]. There is no data directly comparing these agents, so the choice among immunotherapies differs between centers by local practice and cost-effectiveness.

When the studies were evaluated, the median contribution of immunotherapy to overall survival for nivolumab, atezolizumab and pembrolizumab ranged from 9 to 13.8 months [9,12,15,18,20]. In our study, there were no patients who received pembrolizumab. Unlike, our real life experience with

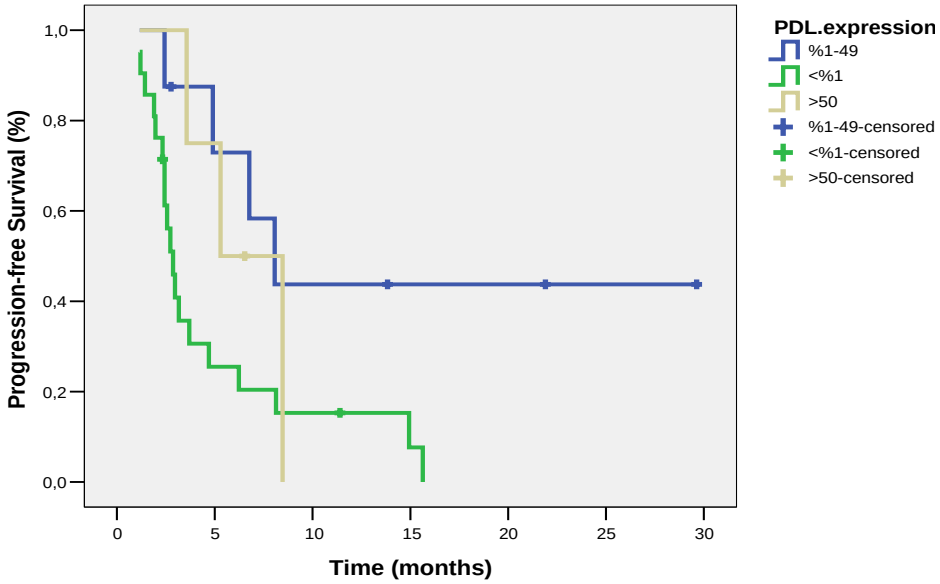

Figure 3: PFS curves according to the PD-L1 expression

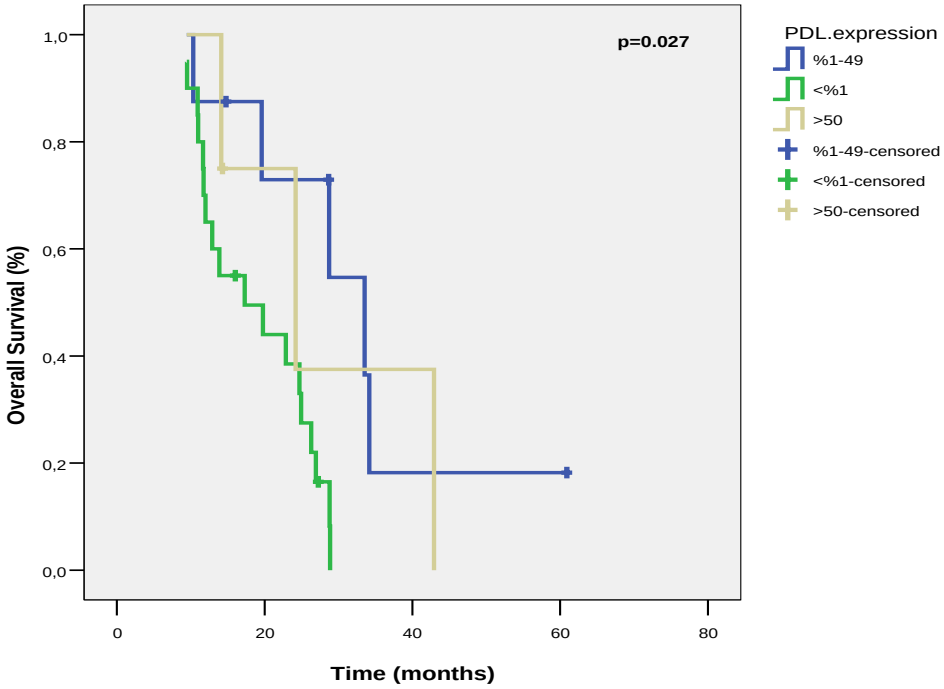

Figure 4: Overall survival curves according to the PD-L1 expression

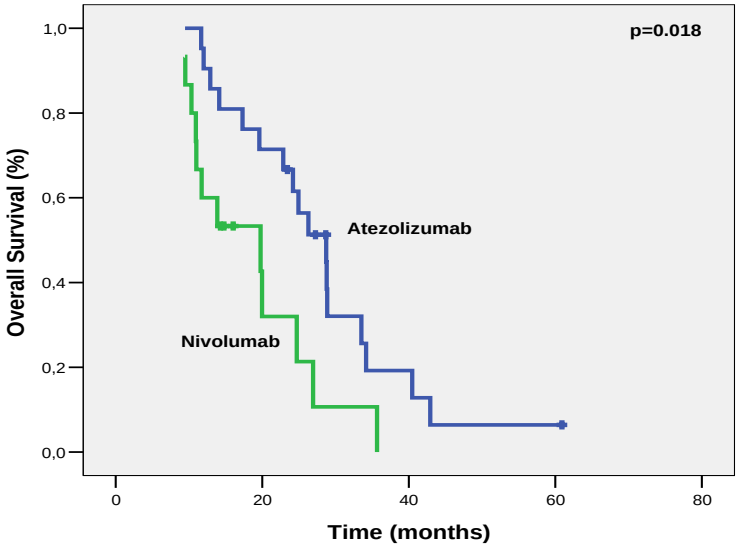

Figure 5: Overall survival curve for patients treated with atezolizumab compared with nivolumab

Table 3: Multivariate analysis for Overall survival and progression-free survival

Factor	X^2	p	HR	95% CI
Overall survival				
Response to immunotherapy	4.29	0.038	5.02	1.09-7.12
Presence of response to first-line chemotherapy	6.23	0.013	0.48	0.27-0.85
Immunotherapy type (Atezo vs Nivo)	4.47	0.034	3.23	1.09-4.09
PD-L1 expression (<1% vs 1-49% vs ≥50%)	3.23	0.072	0.45	0.19-1.07
Presence of brain metastasis	2.94	0.086	0.43	0.16-1.12
Progression-free survival				
Gender	6.98	0.0018	5.18	1.51-7.76
Age (<60 vs ≥60)	6.44	0.003	0.18	0.07-0.72
EGOG PS at the time of immunotherapy (0-1 vs 2)	8.71	0.002	11.3	2.09-19.1
PD-L1 expression (<1% vs 1-49% vs ≥50%)	7.65	0.006	0.32	0.24-0.72
Response to immunotherapy	9.81	0.002	0.26	0.11-0.60
Presence of brain metastasis	0.19	0.65	1.25	0.45-3.47
Presence of response to first-line chemotherapy	0.91	0.33	1.29	0.76-2.17

* HR: hazard ratio, CI: confidence interval, ECOG PS:

nivolumab and atezolizumab is not similar to literature in terms of OS with median 24.1 months. This situation can be explained by the longer median follow-up period and the small sample size. On the other hand, median PFS interval was 4.7 months as similar to the literature [7,12,14]. One of the reasons for the longer overall survival in our study may be associated with the PDL-1 value >1% in 17 of 39 patients. In previous studies, the ORR with nivolumab was 19% in the squamous histological subtype, 20% in the non-squamous subgroup, while the ORR was 14% with atezolizumab [7,12,14]. However, in our study, ORR was 35.1%. Thus, our findings were not compatible with respect to OS and ORR [7,12,14,19]

In our study we showed that PDL-1 expression might differ according to the histologic type of the lung cancer. While PDL-1 positivity was 71.4% in the squamous cell subgroup, it was 52.2% in the group with adenocarcinoma. Similar studies in the literature determined the PDL-1 positivity in tumor cells was 56.2% in squamous cell carcinoma and 39.9% in adenocarcinoma [17]. One possible explanation for this difference may be that PDL-1 positivity is associated with smoking and squamous cell cancer is more frequently associated with smoking [20]. Previously studies showed the response to immunotherapy was worse in tumors with driver mutation [7,12,14]. In our study only three of patients have had driver mutation. Thus, no comment can be made.

Clinical trials in the second line setting included patients with stable brain metastasis [7,14]. As known brain metastasis is related with poor prognosis and in our cohort the number of patients with brain metastasis both at initial diagnosis and during treatment is 15 (4.5%). Although the survival contribution of immunotherapy is uncertain stereotactic radiosurgery was applied all of patients in our study.

An important point in drug preference is cost effectiveness. Under the conditions of our country, the use of Nivolumab 240 mg every two weeks is a more expensive treatment compared to the use of Atezolizumab 1200 mg every 3 weeks. Cost effectiveness is one of the reasons why atezolizumab is preferred more frequently in our center. In our center, 2 patients (5.4%) could not continue treatment due to financial reasons.

In fact there are no clear data to predict immunotherapy treatment response; however the factors found to be associated with longer PFS include; ECOG PS, smoking, liver metastases, lactate dehydrogenase (LDH), and neutrophil-to-lymphocyte ratio(NLR), absence of corticosteroid use and age > 50 years in the literature [23,24]. In our study, gender, age, the presence of brain metastasis, PDL-1 status >1%, ECOG PS and the good response to frontline treatment were found as prognostic factors in univariate analysis for PFS. As well multivariate analysis for PFS revealed that gender (HR: 5.18, p=0.0018), age (HR: 0.18, p=0.003), ECOG PS (HR:11.3, p=0.002), PDL-1 status >1% (HR: 0.32, p=0.006) and good response to immunotherapy (HR:0.26, p=0.002) were significant independent prognostic indicators. However, neither in Phase III CheckMate trials nor in OAK trial PDL-1 status was not found to be prognostic and/or predictive factor for the response [21,22]. Our results were thus not compatible with the literature [21,22].

Treatment-related adverse events of grade 3 or 4 were reported in 7% patients with nivolumab in CheckMate 017 and CheckMate 057 trial; 15% of patients who received atezolizumab in OAK trial [9]. Karak FE et al reported that all-grade immune-related adverse events were reported in around 18% of patients, and were mainly grades 2 and 3 [23]. In our series we reported grade 3-4 adverse events in four patients (10.3%) which was the pneumonitis in three patients, colitis in one patient. Any of treatment related

endocrine side effects were seen in eight of patients (20.3%).

The small sample size and the retrospective design of our study could be considered as significant limitations and might have influenced these results. On the other hand, the long follow-up period and the management of immune-related side effects according to new guidelines were the positive aspects of our study. Therefore, we believe that our findings contribute to the literature, because we analyzed immunotherapy agents in both second and later lines, and in high PDL-1 positive patients with metastatic NSCLC as a single center experience.

In conclusion, our results indicate that both atezolizumab and nivolumab are active agents with good safety profile in second and later lines treatment for patients with metastatic NSCLC. Our real-life data is compatible with the results of previous clinical trials. However, the fact that the effectiveness is in a more PD-L1 positive group shows the need to identify predictive factors necessary to identify patients who will benefit from these drugs in the future.

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