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RESEARCH ARTICLE

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Evaluation of the efficacy and safety of nivolumab in the second- or later-line treatment of patients with locally advanced/metastatic non-small cell lung cancer in Türkiye: a retrospective multicenter non-interventional registry study

Nuri Karadurmus[a], Muhammet Ali Kaplan[b]*, Mehmet Ali Nahit Sendur[c‡], Yuksel Urun[d], Umut Demirci[e§], Saziye Burcak Karaca[f], Sabin Goktas Aydin[g], Musa Baris Aykan[a], Ahmet Bilici[g¶], Ahmet Sezer[h], Ulku Yilmaz[i], Huseyin Abali[j]**, Perran Fulden Yumuk[k‡‡], Serkan Degirmencioglu[l], Ahmet Demirkazik[d], Semra Paydas[m], Cem Mirili[m], Hande Turna[n], Aysegul Kargi[o], Mustafa Ozdogan[o§§], Deniz Can Guven[p], Mustafa Ozguroglu[n] and Saadettin Kilickap[q¶¶]

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ABSTRACT

Objective: To evaluate the efficacy and safety of nivolumab in the second-line (2L) or later-line (LL) treatment of patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) in real-life setting in Türkiye.

Methods: This study was designed as a national, multi-center, retrospective study. The study population was evaluated in two groups for the line of nivolumab therapy: those receiving nivolumab in the 2L (Group 2L) and third-line (3L) or LL (Group 3L/LL). Efficacy was evaluated based on one-year overall survival (OS) and progression-free survival (PFS). Safety was evaluated based on treatment-related adverse events (AEs) and nivolumab discontinuation rate.

Results: Of 244 patients, 52.9% were in Group 2L and 47.1% were in Group 3L/LL. Demographic and clinical characteristics did not differ between the groups. In Group 2L and Group 3L/LL, one-year OS and PFS rates were 60.8% and 61.4% ($p = 0.592$) and 31.2% and 21.3% ($p = 0.078$), respectively. The objective response rate (ORR) was 34.7% in Group 2L and 27.3% in Group 3L/LL ($p = 0.262$). The percentage of patients reporting at least one AE in Groups 2L and 3L/LL was 34.9% and 43.5%, respectively ($p = 0.169$). Fatigue was the most common (16.4%) treatment-related AE in each group. The groups were comparable regarding the AE frequency. Nivolumab was discontinued in 61 patients in Group 2L and 53 patients in Group 3L/LL, with the most common reason being disease progression (57.4% and 66.0%, respectively).

Conclusion: Nivolumab is safe and effective in the 2L or 3L/LL treatment of locally advanced/metastatic NSCLC and associated with acceptable AEs in real-life setting.

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Nivolumab; non-small cell lung cancer; second-line therapy; efficacy; safety

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PLAIN LANGUAGE SUMMARY

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (around 85% of all lung cancers). Patients with NSCLC are usually diagnosed at advanced or metastatic stages. When cancer cells spread to other areas from where they first formed, it is called metastatic cancer. Surgery may not be a treatment option for such patients. Currently, immunotherapeutic agents are used in the treatment of NSCLC. Nivolumab is one of the approved immunotherapeutic agents in the treatment of patients with metastatic NSCLC, who have failed after receiving chemotherapy. Our study explored the efficacy and safety of nivolumab in real-life setting in Türkiye. Nivolumab effectiveness was evaluated by overall survival (OS) and progression-free survival (PFS) rates. OS indicates the proportion of patients who are still alive at a given time after diagnosis or treatment initiation. PFS refers to "the length of time during and after cancer treatment that a person lives with the disease but does not get worse." In the present study, one-year OS for 244 patients who received nivolumab was 61.1% and one-year PFS was 26.4%. Nivolumab safety was evaluated based on the frequency of adverse events observed during nivolumab therapy. Of the patients 38.9% had at least one side effect, with fatigue being the most common (16.4%). Our results support the earlier studies and showed that nivolumab was a safe and effective agent and is associated with acceptable side effects.

Introduction

Lung cancer is a global public health problem and the leading cause of cancer deaths.[1] Histologically, non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers[2,3] and is usually diagnosed at advanced stages. More than half (60%) of patients with lung cancer have locally advanced or metastatic disease (stage III or IV) at diagnosis, and local resection is not an option for such patients.[4,5]

Currently, the use of immunotherapeutic agents alone or in combination with chemotherapy is the standard approach in the first-line treatment of advanced NSCLC.[6] However, their use in first-line (1L) treatment is still limited in some countries due to problems in reimbursement. In such patients, the use of second-line (2L) immunotherapy improves survival compared to the results of single-agent chemotherapy.[7]

In recent years, the treatment of metastatic NSCLC has evolved into more biomarker-driven personalized care along with the inhibition of the programmed cell death protein-1 (PD-1)/programmed cell death protein ligand-1 (PD-L1) pathway, which is an immune checkpoint used by tumor cells to inhibit antitumor responses.[8,9] Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody and specifically binds the PD-1 found on the activated immune cells. It inhibits the receptor to engage with its ligands (PD-L1: B7-H1/CD274 and PD-L2: B7-DC/CD273), and thereby enhances antitumor response of the host.[10,11] Nivolumab was approved by the US Food and Drug Administration (FDA) in March 2015 to be used in the 2L and later-line (LL) treatments of patients with metastatic NSCLC, who showed progression while or after receiving platinum-based chemotherapy.[12] Since then, the efficacy and safety of nivolumab have been documented in various clinical trials. In Türkiye, Bristol-Myers Squibb Pharmaceuticals Inc. received the license for Nivolumab (Opdivo®) in April 2017;[13] however, data from real-life experience in Türkiye remains lacking. The present study aimed to evaluate the efficacy and safety of nivolumab in the 2L or LL treatment of patients with locally advanced/metastatic NSCLC in real-life setting in Türkiye.

Methods

A national, multi-center, retrospective, non-interventional registry study was conducted between July 2015 and October 2021 in the patients diagnosed with locally advanced or metastatic NSCLC at eight centers across Türkiye. The study was conducted after the approval of the University of Health Sciences Gulhane Scientific Researches Ethics Committee (Date: 08.07.2021; Approval No: 2021/251) and in accordance with the Declaration of Helsinki. Male and female patients who were diagnosed with NSCLC in 2015 and later, at the age of $\geq$18 years at the time of initial diagnosis, received nivolumab therapy in the 2L or LL treatment of NSCLC after failure with previous systemic therapy, and had at least 6-month follow-up data prior to nivolumab therapy were considered eligible. Patients with insufficient epidemiological or clinical data were excluded.

The data were retrieved from the patients' medical records and then recorded in the electronic case report forms (eCRFs). The data collected consisted of demographic and clinical characteristics, treatment pattern (duration of nivolumab therapy, reasons for discontinuation, treatment dose adjustment), treatment response by RECIST (*response evaluation criteria in solid tumors*) criteria, and survival status.

Study population was evaluated in two groups according to the line of nivolumab therapy: those receiving nivolumab in the 2L treatment of NSCLC (Group 2L) and those receiving nivolumab in the third-line (3L) or LL treatment of NSCLC (Group 3L/LL). These groups were then compared in terms of safety and efficacy of nivolumab.

Statistical analysis

Data analyses were performed using the Predictive Analytics Software (PASW) 18 (SPSS Inc., Chicago, IL, USA). Normality of data was tested using the visual (histogram and probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Demographic and clinical data were summarized using descriptive statistics. Descriptive statistics were expressed as numbers and percentages for categorical variables and as mean, standard deviation, median, and minimum-maximum for numerical variables. A p value <0.05 was considered the level of statistical significance.

The Kaplan-Meier method was used to assess overall survival (OS) and progression-free survival (PFS). The effects of selected categorical variables (sex, smoking and treatment line) on survival were investigated using the log-rank test. Mann-Whitney U test was used for non-normally distributed

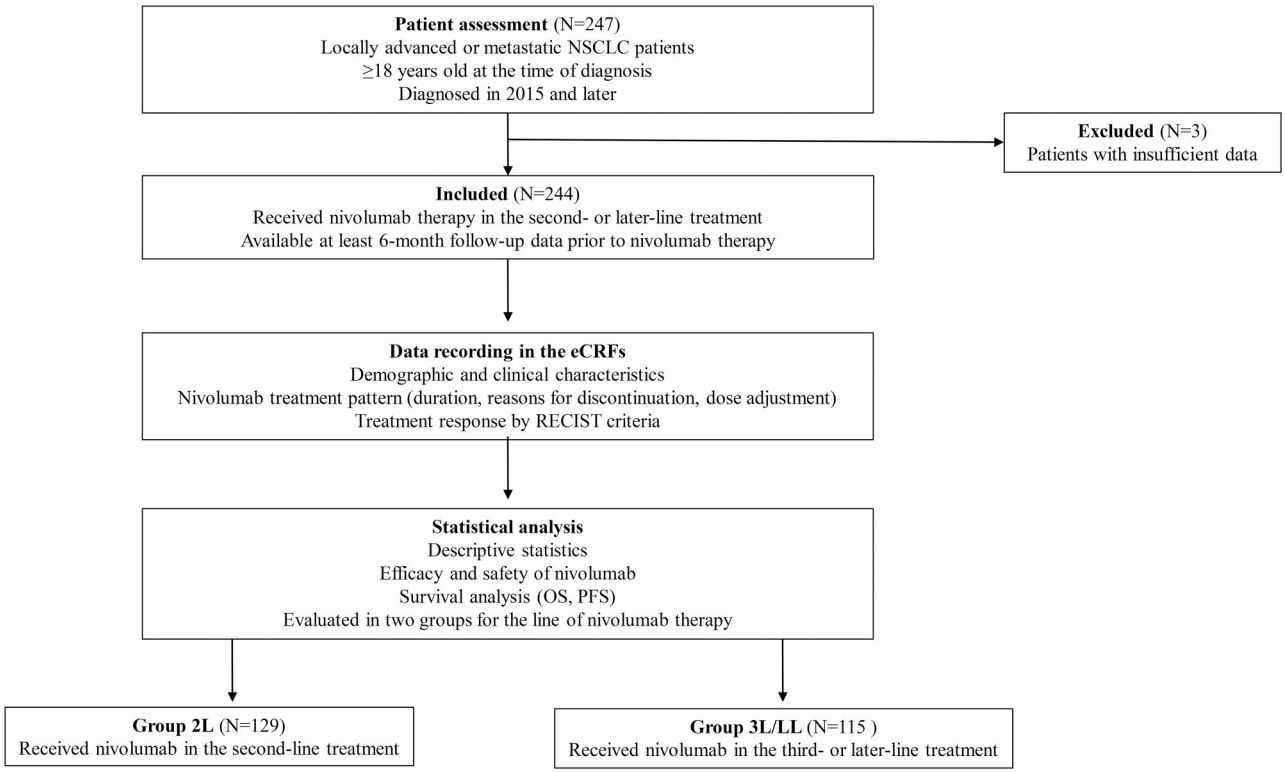


Figure 1. Study flow-chart. NSCLC: non-small cell lung cancer; eCRFs: electronic case report form; RECIST: Response evaluation criteria in solid tumors; OS: overall survival; PFS: progression-free survival; 2L: second-line, 3L/LL: third-line or later-line.

numerical variables. For categorical variables, the Chi-square test was used for two-group and multiple comparisons when Chi-square condition was met, whereas Fisher's exact test was used for two-group and multiple comparisons when Chi-square condition was not met.

Results

Demographic and clinical characteristics

The medical records of 247 patients in eight centers across Türkiye were reviewed; among them, the data of 244 patients were analyzed (Figure 1). Overall, the mean age was 60 ± 10 years, 80.3% were male ($n = 196/244$), 44.3% ($n = 35/79$) were former smokers, and 31.6% ($n = 25/79$) were current smokers (Table 1). The treatment-related information of the whole study population is presented in Table 2. Of the patients, 129 (52.9%) received nivolumab in the 2L and 115 (47.1%) in the 3L or LL treatment of NSCLC.

No significant difference was found between the groups in terms of demographic and clinical characteristics except for lymph node metastasis. Demographic and clinical characteristics according to the line of treatment are summarized in Table 3. Additionally, the molecular characterization (driver mutations) of the population at baseline are summarized in Table 4; no significant difference was found between the groups regarding the frequency of mutations.

Table 1. Demographic and clinical characteristics of patients.

Demographic characteristics	*N*	
Age, year, Mean ± SD	244	60 ± 10
Sex, *n* (%)	244	
Female		48 (19.7)
Male		196 (80.3)
Smoking status, *n* (%)	79	
Nonsmoker		19 (24.1)
Quitted		35 (44.3)
Current smoker		25 (31.6)
Alcohol consumption, *n* (%)	63	
Never consumed		48 (76.2)
Quitted		10 (15.9)
Current consumer		5 (7.9)
Tumor stage, *n* (%)	221	
I-IIIB		38 (17.2)
IV		183 (82.8)
ECOG score, *n* (%)	241	
0		76 (31.5)
1		128 (53.1)
2		34 (14.1)
3		3 (1.2)
Histological type, *n* (%)	216	
Squamous		10 (4.6)
Adenocarcinoma		183 (84.7)
Adenosquamous		14 (6.5)
Unclassified		9 (4.2)
Site of metastasis, *n* (%)	219	
Lungs		105 (47.9)
Liver		31 (14.2)
Brain		36 (16.4)
Lymph node		50 (22.8)
Bones		92 (42.0)
Other		57 (26.0)

2L: second-line, 3L: third-line, LL: later-line, SD: standard deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status.

Efficacy

Regarding the whole study population, the median (minimum-maximum) OS was 18.6 (12.7–23.3) months, with a one-year OS rate of 61.1%. The OS for the whole study population is demonstrated in Figure 2.

Table 2. Treatment-related information of the whole study population ($N = 244$).

Treatment used prior to nivolumab therapy	*n* (%)
Carboplatin + Paclitaxel	25 (10.2)
Pemetrexed + Carboplatin	18 (7.4)
Gemcitabine + Cisplatin	10 (4.1)
Paclitaxel + Cisplatin	9 (3.7)
Cisplatin + Pemetrexed	6 (2.5)
Docetaxel + Cisplatin	3 (1.2)
Carboplatin + Paclitaxel + Radiotherapy	2 (0.8)
Carboplatin + Pembrolizumab	2 (0.8)
Gemcitabine + Carboplatin	2 (0.8)
Carboplatin + NabPaclitaxel	1 (0.4)
Carboplatin + Pemetrexed + Radiotherapy	1 (0.4)
Carboplatin + Radiotherapy	1 (0.4)
Cisplatin + Etoposide	1 (0.4)
Cisplatin + Etoposide + Radiotherapy	1 (0.4)
Cisplatin + Paclitaxel + Radiotherapy	1 (0.4)
Pemetrexed	1 (0.4)
Unknown	160 (65.6)
Nivolumab treatment line, *n* (%)	
Second-line therapy	129 (52.9)
Third- or later-line therapy	115 (47.1)

Table 3. Comparison of demographic and clinical characteristics of the patients in the treatment line groups.

Characteristics	Group 2L	Group 3L/LL	*p*
Age, year, Mean ± SD	61 ± 10	59 ± 10	0.181*
Median (minimum-maximum)	61 (31-86)	60 (34-79)	
Sex, *n* (%)			
Female	23 (17.8)	25 (21.7)	0.443**
Male	106 (82.2)	90 (78.3)	
Smoking status, *n* (%)			
Nonsmoker	12 (22.2)	7 (28.0)	0.822**
Quitted	25 (46.3)	10 (40.0)	
Current smoker	17 (31.5)	8 (32.0)	
Alcohol consumption, *n* (%)			
Never consumed	34 (75.6)	14 (77.8)	1.000***
Quitted	7 (15.6)	3 (16.7)	
Current consumer	4 (8.9)	1 (5.6)	
Tumor stage, *n* (%)			
Stage I-IIIB	21 (17.8)	17 (16.5)	0.800**
Stage IV	97 (82.2)	86 (83.5)	
ECOG score, *n* (%)			
0	38 (29.5)	38 (33.9)	0.263***
1	67 (51.9)	61 (54.5)	
2	21 (16.3)	13 (11.6)	
3	3 (2.3)	0 (0)	
Histologic type, *n* (%)			
Squamous	3 (2.7)	7 (6.8)	0.076***
Adenocarcinoma	95 (84.1)	88 (85.4)	
Adenosquamous	7 (6.2)	7 (6.8)	
Unclassified	8 (7.1)	1 (1.0)	
Site of metastasis, *n* (%)			
Lungs	56 (45.9)	49 (50.5)	0.497**
Liver	19 (15.6)	12 (12.4)	0.499**
Brain	18 (14.8)	18 (18.6)	0.451**
Lymph node	38 (31.1)	12 (12.4)	**0.001****
Bones	50 (41)	42 (43.3)	0.730**
Other	34 (27.9)	23 (23.7)	0.486**

*Mann-Whitney U test.
**Chi-square test. Bold value is significant at $p < 0.05$.
***Fisher's exact test.
2L: second-line, 3L/LL: third-line or later-line, SD: standard deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status.

One-year OS rates in Group 2L and Group 3L/LL were 60.8% and 61.4%, respectively. The median (minimum-maximum) OS was 22.0 (12.7–31.3) months for Group 2L and 17.8 (13.3–23.3) months for Group 3L/LL. OS showed no significant difference between the two groups ($p = 0.592$) (Figure S1). No difference was observed in OS according to smoking status or sex (Figures S2 and S3).

Table 4. Comparison of molecular characteristics (driver mutations) of the patients in the treatment line groups.

Driver mutations	All patients	Group 2L	Group 3L/LL	*p*
EGFR	12 (14.5)	6 (10.5)	6 (23.1)	0.179**
ALK	12 (14.3)	6 (10.3)	6 (23.1)	0.176**
ROS-1	10 (12.0)	6 (10.5)	4 (15.4)	0.717**
BRAF	9 (11.1)	4 (7.1)	5 (20.0)	0.126**
KRAS	5 (6.2)	2 (3.6)	3 (12.0)	0.168**
PD-L1	37 (44.0)	26 (44.8)	11 (42.3)	0.830*

*Chi-square test.
**Fisher's exact test.
2L: second-line treatment, 3L/LL: third-line or later-line treatment.

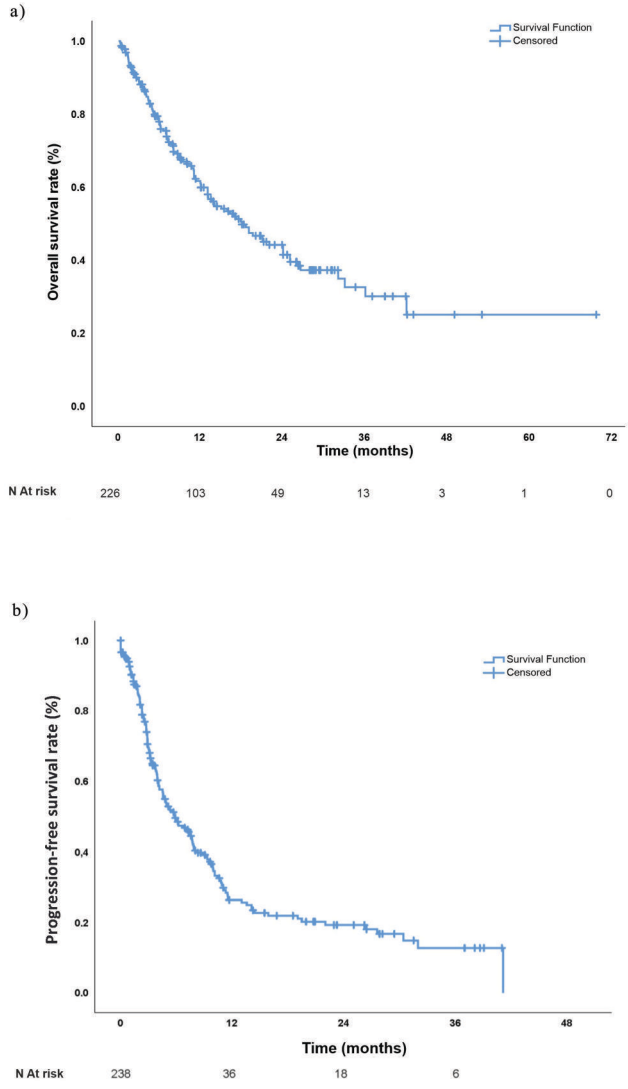


Figure 2. (a) Overall survival and (b) Progression-free survival curve for the whole study population.

In the whole study population, the one-year PFS rate was 26.4%, with a median PFS of 5.85 (3.91–7.79) months (Figure 2).

The one-year PFS rate was 31.2% for Group 2L and 21.3% for Group 3L/LL, with a median PFS of 7.75 (5.21–10.30) months and 4.63 (3.91–7.79) months, respectively. The PFS showed no significant difference between the treatment line groups ($p = 0.078$) (Figure S4). No difference was observed in PFS according to smoking status or sex (Figures S5 and S6).

Table 5. Treatment response rates by RECIST criteria according to the treatment line groups.

	All patients $N = 189$ n (%)	Group 2L $N = 101$ n (%)	Group 3L/LL $N = 88$ n (%)	
Complete response (CR)	7 (3.7)	4 (4.0)	3 (3.4)	0.264*
Partial response (PR)	52 (27.5)	31 (30.7)	21 (23.9)	
Stable disease (SD)	26 (13.8)	17 (16.8)	9 (10.2)	
Progressive disease (PD)	104 (55.0)	49 (48.5)	55 (62.5)	
Objective response rate (ORR)	59 (31.2)	35 (34.7)	24 (27.3)	0.275**

*Fisher's exact test.
**Chi-square.
RECIST: Response evaluation criteria in solid tumors, 2L: second-line, 3L/LL: third-line or later-line.

In the whole study population, the response rates (RRs) per RECIST were available in 189 patients (101 patients in Group 2L and 88 patients in Group 3L/LL) (Table 5). In those patients, 59 had a response, resulting in an ORR of 31.2%; 3.7% showed complete response (CR), 27.5% showed partial response (PR), 13.8% had stable disease (SD), and 55.0% had progressive disease (PD). The RRs did not differ between the groups ($p = 0.264$). The ORR was 34.7% ($n = 35$) in Group 2L and 27.3% ($n = 24$) in Group 3L/LL, with no significant difference between the groups ($p = 0.275$).

Safety

Among all patients, 38.9% ($n = 95$) reported at least one adverse event (AE) of any grade during nivolumab therapy, with fatigue being the most common AE (16.4%), followed by toxicity (14.6%), poor appetite (11.8%), and anemia (11.6%). In Group 2L and Group 3L/LL, the rate of patients reporting at least one AE of any grade was 34.9% and 43.5%, respectively, and the difference was not statistically significant ($p = 0.169$). The groups were comparable in terms of the frequency of AEs excluding skin rash, which was significantly higher in Group 3L/LL as compared to Group 2L (5.6% vs. 0%) ($p = 0.009$) (Table 6).

Nivolumab therapy was discontinued in 114 patients (46.7%) (61 in Group 2L and 53 in Group 3L/LL). The most common reason for discontinuation of nivolumab therapy was disease progression in both Group 2L and Group 3L/LL (57.4% and 66.0%, respectively) (Table 7).

Discussion

In the present study, we evaluated the safety and efficacy of nivolumab used in the 2L and 3L/LL treatment of patients with locally advanced and metastatic NSCLC on the basis of real-life data. The treatment line groups were comparable in terms of demographic and clinical characteristics. We found that nivolumab therapy is associated with improved OS and PFS rates and low AE rates regardless of treatment line.

According to the 2021 cancer statistics, the lung cancer survival rate is low with a median 5-year survival rate being 6% for metastatic disease and 59% for localized disease in the US.[14] The development of immune checkpoint inhibitors completely changed the treatment paradigm. Improved survival is reported in considerably more patients with metastatic NSCLC treated with immune checkpoint inhibitors than with chemotherapy alone.[7]

Nivolumab (BMS-936558/ONO-4538) was the first PD-1-specific monoclonal antibody and initially approved in 2015 for the 2L treatment of advanced/metastatic NSCLC after failure with 1L chemotherapy.[15] The approved indications have been moved to earlier lines and extended to the other types of cancer in a relatively short period of time. In two phase III studies, nivolumab monotherapy was associated with statistically superior survival benefit compared to docetaxel, which was the standard of care at the time of trials in 2L treatment of patients with advanced NSCLC with failure to previous treatment.[16,17]

Efficacy

Approval of nivolumab for the treatment of patients with advanced NSCLC was based on two Phase 3 trials (CheckMate 057 and CheckMate 017), which showed survival benefit over docetaxel across histological types.[16,17] So far, a number of clinical trials on nivolumab have demonstrated satisfactory efficacy with improved OS and PFS rates in the treatment of patients with NSCLC as described below. Both three-year outcomes from CheckMate 057 and CheckMate 017 studies[18] and the results of a pooled analysis of ONO-4538-05 and ONO-4538-06 studies[19] revealed durable responses in some of the patients with NSCLC.

A real world study from Israel, where the majority (64%) of patients received nivolumab in the 2L treatment, reported a median OS of 5.9 months (95% CI 4.7–7.4) with Eastern Cooperative Oncology Group Performance Status (ECOG PS) being the only variable significantly associated with OS. The response, which was evaluated in 49 patients, revealed an ORR of 35% and a median PFS of 2.8 months (95% CI, 1.8–7.7).[20] A systematic review of 11 randomized controlled clinical trials (RCTs) on 7,581 patients comparing the efficacy and safety of licensed 2L treatments including the checkpoint inhibitors nivolumab, atezolizumab and pembrolizumab in patients with advanced-stage NSCLC reported superior OS benefit over docetaxel and determined that nivolumab was associated with the highest survival benefit compared to atezolizumab and pembrolizumab (based on a meta-analysis and not on head-to-head trial comparison).[15] PFS benefit was also the highest with nivolumab therapy. Moreover, nivolumab was found significantly safer as compared to atezolizumab and pembrolizumab. Nivolumab, pembrolizumab and atezolizumab exhibited superior benefit/risk balance compared to other licensed drugs used in advanced-stage NSCLC.[15] In another study investigating the long-term efficacy and safety of nivolumab in 129 patients with advanced NSCLC pretreated with $\geq$3 prior therapies, nivolumab showed durable clinical activity with a median OS of 9.9 months and with one-year and two-year OS rates of 42% and 24%, respectively.[21] A study from Japan investigated 901 patients with NSCLC, the majority of whom received nivolumab as 2L treatment.[22] In that study, the median OS (14.6 months), one-year survival rate (54.3%) and the median

Table 6. Frequency of adverse events according to the treatment line groups.

	All patients		Group 2L		Group 3L/LL		
Adverse Events	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	*p*
Presence of at least 1 adverse event	244	95 (38.9)	129	45 (34.9)	115	50 (43.5)	0.169*
Fatigue	238	39 (16.4)	127	19 (15.0)	111	20 (18.0)	0.525*
Toxicity	240	35 (14.6)	129	16 (12.4)	111	19 (17.1)	0.302*
Poor appetite	238	28 (11.8)	128	13 (10.2)	110	15 (13.6)	0.406*
Anemia	241	28 (11.6)	127	12 (9.4)	114	16 (14.0)	0.267*
Elevated creatinine	238	13 (5.5)	126	5 (4)	112	8 (7.1)	0.282*
Hypothyroidism	224	12 (5.4)	119	7 (5.9)	105	5 (4.8)	0.710*
Lymphopenia	238	12 (5.0)	126	7 (5.6)	112	5 (4.5)	0.701*
Pneumonitis	237	9 (3.8)	125	5 (4.0)	112	4 (3.6)	1.000**
Nausea	238	8 (3.4)	127	3 (2.4)	111	5 (4.5)	0.478**
Elevated ALT/AST	237	7 (3.0)	125	3 (2.4)	112	4 (3.6)	0.710**
Pruritus	239	7 (2.9)	128	2 (1.6)	111	5 (4.5)	0.255**
Rash/skin toxicity	230	6 (2.6)	123	0 (0.0)	107	6 (5.6)	**0.009****
Neutropenia	239	5 (2.1)	126	4 (3.2)	113	1 (0.9)	0.373**
Elevated amylase	189	4 (2.1)	109	2 (1.8)	80	2 (2.5)	–
Elevated lipase	187	4 (2.1)	108	3 (2.8)	79	1 (1.3)	–
Diarrhea/Colitis	238	4 (1.7)	127	3 (2.4)	111	1 (0.9)	–
Hypercalcemia	240	4 (1.7)	126	2 (1.6)	114	2 (1.8)	–
Arthralgia	244	3 (1.2)	129	3 (2.3)	115	0 (0.0)	–
Hypophosphatemia	187	2 (1.1)	107	1 (0.9)	80	1 (1.3)	–
Fever	237	2 (0.8)	126	1 (0.8)	111	1 (0.9)	–
Hypocalcemia	237	2 (0.8)	126	1 (0.8)	111	1 (0.9)	–
Hypophysitis	244	2 (0.8)	129	1 (0.8)	115	1 (0.9)	–
Hyperthyroidism	244	2 (0.8)	129	2 (1.6)	115	0 (0.0)	–
Thyroiditis	244	2 (0.8)	129	2 (1.6)	115	0 (0.0)	–
Neuropathic pain	244	2 (0.8)	129	0 (0.0)	115	2 (1.7)	–
Adrenal insufficiency	244	2 (0.8)	129	1 (0.8)	115	1 (0.9)	–
Elevated CPK	189	1 (0.5)	109	1 (0.9)	80	0 (0.0)	–
Abdominal pain	244	1 (0.4)	129	0 (0.0)	115	1 (0.9)	–
Pancreatitis	237	1 (0.4)	126	1 (0.8)	111	0 (0.0)	–
Stomatitis/dry mouth	239	1 (0.4)	127	0 (0.0)	112	1 (0.9)	–
Infusion-induced hypersensitivity reaction	228	1 (0.4)	125	0 (0.0)	103	1 (1)	–
Thrombocytopenia	238	1 (0.4)	125	0 (0.0)	113	1 (0.9)	–
Deep vein thrombosis	244	1 (0.4)	129	1 (0.8)	115	0 (0.0)	–

*Chi-square test.
**Fisher's exact test. Bold value is significant at $p < 0.05$.
2L: second-line, 3L/LL: third-line or later-line, ALT/AST: alanine transaminase/aspartate aminotransferase CPK: creatine phosphokinase.

Table 7. Reasons for discontinuation of nivolumab therapy.

Reasons	All patients *N* = 114 *n* (%)	Group 2L *N* = 61 *n* (%)	Group 3L/LL *N* = 53 *n* (%)	*p*
Disease progression	70 (61.4)	35 (57.4)	35 (66.0)	0.343*
No response	17 (14.9)	11 (18)	6 (11.3)	0.316*
Toxicity	4 (3.5)	1 (1.6)	3 (5.7)	-**
Patient's decision	1 (0.9)	0 (0)	1 (1.9)	-**
Other	22 (19.3)	14 (23)	8 (15.1)	0.289*

*Chi-square test.
**Could not analyzed due to insufficient sample size.
2L: second-line, 3L/LL: third-line or later-line.

PFS (2.1 months) were lower than those found in our study, which found a median OS of 18.6 months; one-year OS of 61.1%; and a median PFS of 5.85 months.

In a study investigating the real-world experience with nivolumab in 58 patients with NSCLC of any histological subtype, who have received ≥2 prior therapies, the median OS was lower than that found in the present study (11.7 months vs. 18.6 months). Of the patients, 46.6% were alive at the time of data cut-off. No difference was determined between 1 vs. >1 prior lines of therapy in terms of OS.[23]

In two studies, despite shorter PFS, favorable OS benefit was reported with nivolumab therapy during median 17 to18-month follow-up period.[7,24] No statistically significant differences were detected between sexes, according to age groups, histological subtypes or number of prior treatment lines.[7]

Smoking is the major risk factor and related to 80–90% of deaths from lung cancer.[25] In Türkiye, smoking is responsible for 90% of lung cancer cases.[26] Nishio et al.[27] reported better treatment response with 3 mg/kg nivolumab therapy after failure with platinum-containing chemotherapy in current/former smokers vs. nonsmokers with advanced or recurrent non-squamous NSCLC. Similarly, Morita et al.[22] reported that smoking is associated with better PFS. However, the present study found no significant correlation of OS or PFS with smoking status although OS seemed to be improved, which was consistent with that reported by Areses Manrique et al.[7] In two studies, each of PR, SD and PD were reported in around one-third of the patients with NSCLC, with only 1.4%[24] and 1.6%[7] showing CR. In another study, 14.5% of the patients with advanced, refractory, squamous NSCLC showed objective response (assessed by an independent radiology review committee) and 26% had SD, supporting the efficacy of nivolumab reported in randomized, controlled, phase 3 studies of 1L and 2L treatment.[28] In the present study, however, ORR was higher by half (31.2%), but the rate of SD was lower by half (13.8%). These differences might be due to the differences in samples sizes, nivolumab doses and/or study designs.

Safety

In the literature, the frequency of observing at least one AE during nivolumab therapy were reported at a rate between 58% and 84%.[7,17,24,27,28] Nevertheless, most of the AEs were low-grade AEs with discontinuation of the nivolumab due to treatment-related AEs being as low as <5%.[7,17] In our study, the frequency of at least one AE during nivolumab therapy was found to be lower (38.9%) probably due to its retrospective nature. Fatigue has been reported as the most common AE during the nivolumab therapy ranging from 16% to 33%.[7,17,24,28] Similarly, we also found fatigue as the most common AE (16.4%) in our study population.

As in many retrospective studies, this study also has some limitations. First, there were missing data in the patients' medical records, which may limit the interpretation of the analyses. Second, duration of follow-ups showed significant variability among patients, leading to a difficulty in interpreting the outcomes of interest. In addition, the safety and efficacy of nivolumab were not compared between the histological subtypes. Therefore, it is difficult to draw a definite and generalizable conclusion from our results. Nevertheless, this is the first study demonstrating safety and efficacy of nivolumab in patients with NSCLC in a real-life setting in Türkiye, contributing to the world-wide limited data from real-life.

Conclusion

Our results are consistent with earlier studies and showed that nivolumab was a safe and effective agent to be used in the 2L or LL treatment of patients with locally advanced or metastatic NSCLC after failure with chemotherapy or systemic therapy regardless of the number of prior therapies, and that it is associated with acceptable AEs. Further prospective studies investigating all checkpoint inhibitors, as well as switching between two different checkpoint inhibitors, in larger cohorts are required.

Transparency

Declaration of funding

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Declaration of financial/other relationships

Huseyin Abali has received lecture and meeting support from BMS and participated in Advisory Board for BMS. Perran Fulden Yumuk has participated in Advisory Board for Amgen, GSK, BMS, Roche, and Pfizer and has received support for attending meetings and/or travel from Astra Zeneca, BMS, and Roche and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Amgen. Mustafa Ozguroglu has received consulting fees from Astellas, Regeneron, Sanofi; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Regeneron; payment for expert testimony from Astra Zeneca, support for attending meetings and/or travel from Regeneron; has participated in a Data Safety Monitoring Board or Advisory Board for MSD; have taken part in Steering Board for Astra Zeneca and Bayer. Saadettin Kilickap has received support for travel from Regeneron. All other authors have declared no conflicts of interest. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Nuri Karadurmus: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing; Muhammet Ali Kaplan: Investigation, Writing - review & editing; Mehmet Ali Nahit Sendur: Investigation, Writing - review & editing; Yuksel Urun: Investigation, Writing - review & editing; Umut Demirci: Investigation, Writing - review & editing; Saziye Burcak Karaca: Investigation, Writing - review & editing; Sabin Goktas Aydin: Investigation, Writing - review & editing; Baris Aykan: Investigation, Writing - review & editing; Ahmet Bilici: Investigation, Writing - review & editing; Ahmet Sezer: Investigation, Writing - review & editing; Ulku Yilmaz: Investigation, Writing - review & editing; Huseyin Abali: Investigation, Writing - review & editing; Perran Fulden Yumuk: Investigation, Writing - review & editing; Serkan Degirmencioglu: Investigation, Writing - review & editing; Ahmet Demirkazik: Investigation, Writing - review & editing; Semra Paydas: Investigation, Writing - review & editing; Cem Mirili: Investigation, Writing - review & editing; Hande Turna: Investigation, Writing - review & editing; Aysegul Kargi: Investigation, Writing - review & editing; Mustafa Ozdogan: Investigation, Writing - review & editing; Deniz Can Guven: Investigation, Writing - review & editing; Mustafa Ozguroglu: Investigation, Writing - review & editing; Saadettin Kilickap: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Roles/Writing - original draft, Writing - review & editing.

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