Real-world efficacy and safety data of immune checkpoint inhibitors in Turkish patients with metastatic melanoma: A Turkish oncology group retrospective study

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Abstract. In recent years, significant success has been achieved in the treatment of metastatic melanoma with the use of immune checkpoint inhibitors (ICIs), and it resulted in a remarkable increase in patient survival. However, there are only a few studies reflecting daily practice outside of clinical trials. The present study aimed to evaluate the effectiveness and safety of ICI therapy in Turkish patients with metastatic melanoma, including those with poor prognostic factors such as advanced age and brain metastasis.

A retrospective analysis was conducted on 249 patients diagnosed with metastatic melanoma and treated with ICIs at

23 cancer centers in Turkey. The efficacy and safety of treatment were investigated, and prognostic factors were examined.

The mean age was 59 years, and 64% of patients were male. A total of 28% had BRAF mutation. A total of 22% of the patients were >70 years of age and 26% had brain metastases. The objective response rate with ICI therapy was 37.7%. The median overall survival (OS) was 61 months (95% CI 47-74.9), and the median progression-free survival was 7 months (95% CI 5.9-8). Examining factors influencing overall survival, the difference in median OS was not statistically significant by sex and BRAF status, whereas there were statistically significant differences by age, objective response status, metastasis pattern, and presence of brain metastasis. Median OS was 35 months in patients >70 years when compared with 67 months in patients aged 70 years and younger (P=0.02). Median OS was 41 months in patients without objective response, whereas it could not be reached in patients with objective response (P<0.0001). Median OS was 35 months in patients with *de novo* metastatic disease compared with 78 months in patients with recurrent metastasis (P<0.0001). Moreover, median OS was 37 months in patients with brain metastasis in comparison with 67 months in patients without brain metastasis (P=0.006). Multivariate analysis revealed that absence of objective response, presence of *de novo* metastasis, and presence of brain metastasis were independent poor prognostic factors affecting survival. Grade 3-4 immune-related adverse effects were observed in 7.2% of patients, and treatment was discontinued due to adverse effects in 2.8% of patients. The present study demonstrated that real-world data on ICI therapy in Turkish patients with metastatic melanoma may slightly differ from the results of other studies due to Turkey's conditions. Additionally, the present study, which included non-clinical trial patients, revealed important prognostic factors.

Introduction

Melanoma, while comprising only 4% of all skin cancers, accounts for 80% of all skin cancer-related deaths (1). Response to chemotherapy is poor in metastatic melanoma, with an objective response rate (ORR) of ~10% (2). Immunotherapy and targeted therapy are new treatment modalities used in melanoma, found to be more effective than chemotherapy, thus changing the treatment paradigm for melanoma. Immune checkpoint inhibitors (ICIs) are used in immunotherapy for melanoma. These ICIs are Ipilimumab, Pembrolizumab and Nivolumab. Ipilimumab is a monoclonal antibody targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4), whereas Pembrolizumab and Nivolumab are monoclonal antibodies targeting the programmed death 1 (PD-1).

ICI therapy in metastatic melanoma demonstrates its efficacy independently of BRAF mutation status and programmed death-ligand 1 (PD-L1) status, and the response persists in the long term in patients who respond (3).

Anti-PD-1 blockade in metastatic melanoma is the new standard primary treatment. The 5-year long-term results of the KEYNOTE-006 study exhibited significant differences in ORR, progression-free survival (PFS) and overall survival (OS) in the Pembrolizumab arm compared with Ipilimumab arm in the first-line treatment. The 5-year OS was 32.7 months in the Pembrolizumab arm compared with 15.7 months in the Ipilimumab arm (HR: 0.73, 95%; CI: 0.61-0.88) (4). The efficacy of Nivolumab was demonstrated in the 5-year long-term results of the CheckMate 066 study. The 5-year OS rate was 39% in the Nivolumab arm when compared with 17% in the Dacarbazine arm (5). In the long-term results of the CheckMate 067 study, which investigated Ipilimumab + Nivolumab combination therapy, the median OS was 36.9 months in the Nivolumab arm when compared with 72.1 months in the Ipilimumab + Nivolumab combination arm (6).

The study conducted by Abali *et al* (7) in 2015 as a Turkish Oncology Group project, which analysed data from 1,157 Turkish patients with cutaneous melanoma, was highly significant and pioneering in this field in Turkey. The patients in that study presented with more advanced stages and they had worse prognosis compared with SEER database (1). Another study conducted by Urun *et al* (8) in 2019, which investigated prognostic factors in 97 patients with metastatic melanoma treated with Ipilimumab in Turkey, was an important study in this field in Turkey. In this retrospective study presenting real-world data, the median OS was found to be 9.7 months.

Regarding the use of ICIs in metastatic melanoma, studies reflecting daily practice outside of clinical trials are limited. Moreover, numerous clinical trials do not include elderly patients or patients with brain metastasis.

The present study aimed to examine the effectiveness and safety of ICI therapy in Turkish patients with metastatic melanoma outside of clinical trials and to report real-life data. Among the patients included in the present study, there were those with poor prognostic factors such as advanced age or brain metastasis.

Materials and methods

The present study was a retrospective multicenter observational study, which involved a total of 249 patients who received ICI therapy for metastatic melanoma diagnosis between June 2013 and April 2021 at 23 cancer centers in Turkey. The present multicenter retrospective study was approved by the Ethics Committee of University of Health Sciences (approval no. 05.04.2021-25877). Patient data were collected from the medical records of participating oncology centers. Patient generic consent for the use of the data was obtained at the time of admission. The inclusion criteria of the present study were as follows: Age, >18 years old; having a diagnosis of cutaneous melanoma; and receiving at least one cycle of ICI therapy for metastatic melanoma. The exclusion criteria of the present study were being <18 years old and having a diagnosis of acral or mucosal melanoma. The single-agent Ipilimumab dose was 3 mg/kg IV every 21 days for 4 cycles, the single-agent Nivolumab dose was 240 mg/day IV every 14 days. In the Ipilimumab and Nivolumab combination therapy, the Ipilimumab dose was 3 mg/kg IV every 21 days for 4 cycles, the Nivolumab dose was 1 mg/kg IV every 21 days for 4 cycles, then the Nivolumab dose was 240 mg/day IV every 14 days. Patients were aged 18 years or older, Stage 4, and had an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients were staged according to the American Joint Committee on Cancer (AJCC) Cancer Staging System. Patients diagnosed before 2018 were staged according to the

AJCC 7th edition (published in 2010), and patients diagnosed after 2018 were staged according to the AJCC 8th edition (published in 2018). Treatment response was evaluated by using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 criteria.

Statistical analyses. Descriptive statistics were used to characterize patient and treatment features. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. The Cox proportional hazards model was employed to examine factors influencing survival. P<0.05 was considered to indicate a statistically significant difference. Statistical analysis was conducted using SPSS Statistics version 22 (IBM Corp.).

Results

Patient characteristics. In the present study, 249 patients with metastatic melanoma, who received ICI therapy between June 2013 and April 2021 at 23 cancer centers in Turkey, were included. Patient characteristics are summarized in Table I. The mean follow-up period was 61 months (range 47.1-74.9 months). The median age was 61 years (range 19-88 years). Of the patients included in the present study, 159 were male (63.9%) and 90 were female (36.1%). BRAF mutation was found in 28.1% of patients. A total of 22% of the patients were >70 years of age and 26% had brain metastases.

When examined by the mode of metastasis occurrence, 43% of patients had *de novo* metastasis, and 57% had recurrent metastasis. Among the patients, 32.1% were classified as M1a, 28.5% as M1b, 21.7% as M1c and 17.7% as M1d. Elevated serum LDH levels were found in 44.6% of patients. A total of 21% of patients received ICI therapy in the first-line therapy, while 79% received it in the second-line therapy. A total of 69.5% of patients received Nivolumab, 28.1% received Ipilimumab and 2.4% received Ipilimumab + Nivolumab therapy.

Effectiveness. Objective response was observed in 94 patients receiving ICI therapy, and the ORR was found to be 37.7%. Complete response (CR) was observed in 28 patients (11.2%), partial response (PR) in 66 patients (26.5%), stable disease in 29 patients (11.6%) and progression disease in 123 patients (50.6%). Disease control rate was found to be 49.3%. The effectiveness data is summarized in Table II.

Median OS was found to be 61 months (95% CI 47-74.9) (Fig. 1), while median PFS was 7 months (95% CI 5.9-8).

Median OS was 55 months in men, and 65 months in women. Median OS was 67 months for patients with BRAF mutation, while it was 65 months for BRAF wild-type patients. There was no statistically significant difference in median OS by sex and BRAF status.

Median OS was 35 months for patients aged >70 years and 67 months for patients aged 70 years and younger. This difference was determined to be statistically significant (P=0.02). While the median OS was found to be 41 months in patients without objective response, it could not be reached in patients with objective response. This difference was statistically significant (P<0.0001) (Fig. 2). Median OS was 35 months for patients with *de novo* metastasis, while it was 78 months for patients with recurrent metastasis. This difference was found to be statistically significant (P<0.0001) (Fig. 3). Median OS was 37 months for patients with brain metastasis, and

Table I. Baseline characteristics of patients.

Characteristics	n=249
Age, years	
Median	61
Range	19-88
Sex	
Male	159 (63.9%)
Female	90 (36.1%)
ECOG performance status	
0	33 (13.3%)
1	165 (66.3%)
2	51 (20.4%)
BRAF mutation	
Mutated	70 (28.1%)
No mutation	179 (71.9%)
Brain metastasis	
Yes	65 (26.1%)
No	184 (73.9%)
Metastasis status	
De novo	107 (43%)
Recurrent	142 (57%)
Lactate dehydrogenase	
Elevated	111 (44.6%)
Normal	138 (55.4%)
Stage	
M1a	80 (32.1%)
M1b	71 (28.5%)
M1c	54 (21.7%)
M1d	44 (17.7%)
Treatment modality	
Nivolumab	173 (69.5%)
Ipilimumab	70 (28.1%)
Ipilimumab + Nivolumab	6 (2.4%)

Table II. Response rates to immune checkpoint inhibitors.

Best overall response	n=249
CR	28 (11.2%)
PR	66 (26.5%)
SD	29 (11.6%)
PD	123 (50.6%)
ORR (CR + PR)	94 (37.7%)
DCR (CR + PR + SD)	123 (49.3%)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

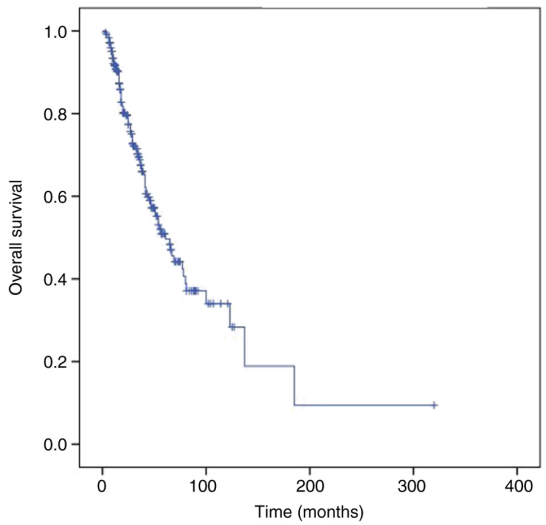

Figure 1. Kaplan-Meier analysis of the overall survival for all patients.

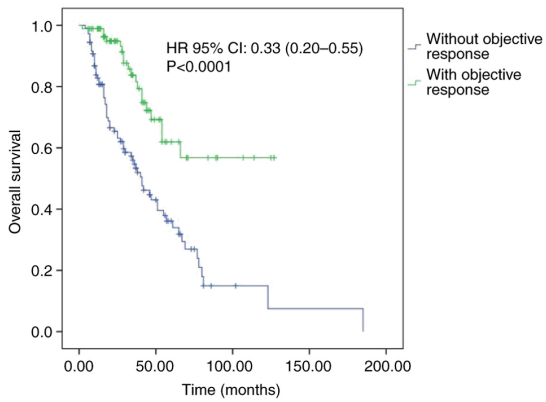

Figure 2. Kaplan-Meier analysis of the overall survival according to objective response status.

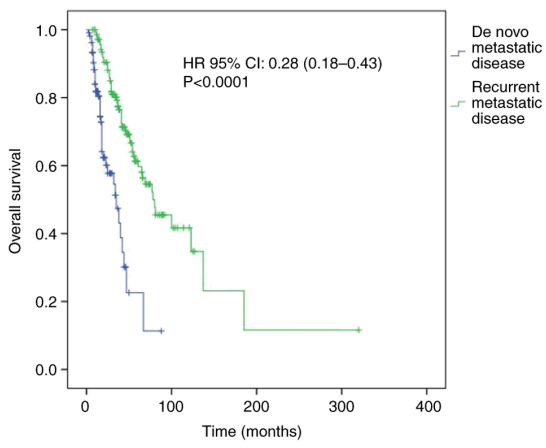

Figure 3. Kaplan-Meier analysis of the overall survival according to metastasis pattern.

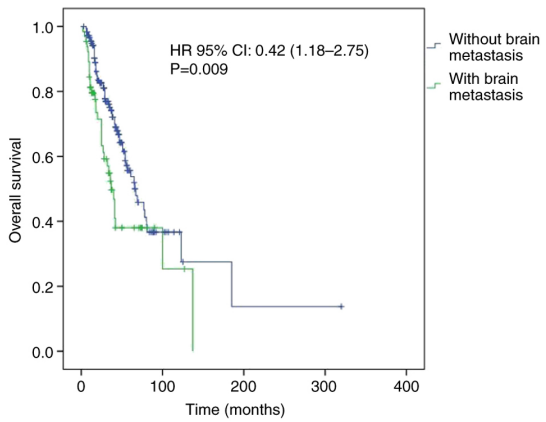

Figure 4. Kaplan-Meier analysis of the overall survival according to presence of brain metastasis.

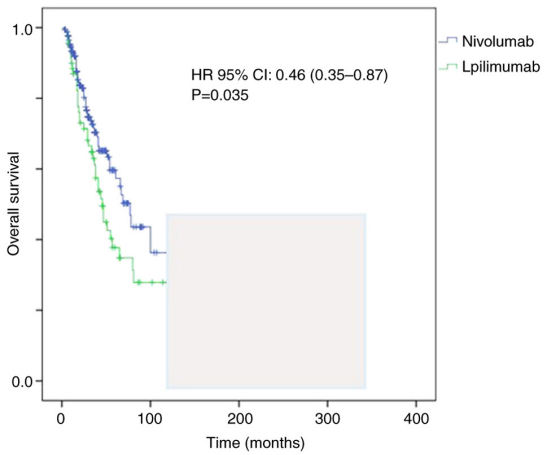

Figure 5. Kaplan-Meier analysis of the overall survival according to immune checkpoint agent.

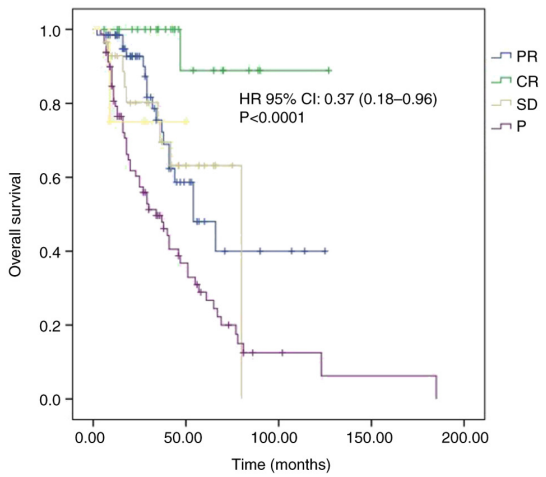

Figure 6. Kaplan-Meier analysis of the overall survival according to response to treatment.

67 months for patients without brain metastasis. This difference was statistically significant (P=0.006) (Fig. 4). Median OS was 77 months in patients receiving Nivolumab and 46 months in patients receiving Ipilimumab. The difference was statistically significant (Fig. 5). When evaluated according to treatment response, the median OS had not yet been reached in patients with CR, whereas it was 54 months in those with

Table III. Uni-and multi-variable analysis.

	Univariable analysis		Multivariable analysis	
Variable	HR for death (95% CI)	P-value	HR for death (95% CI)	P-value
Sex	1.09 (0.62-1.95)	0.757		
BRAF status	1.12 (0.73-2.01)	0.720		
Age (<70 or >70)	1.20 (1.13-1.28)	0.02	0.59 (0.90-2.50)	0.118
Objective response	0.33 (0.20-0.55)	<0.0001	0.36 (0.21-0.60)	<0.0001
Type of metastasis (*De novo* or recurrence)	0.28 (0.18-0.43)	<0.0001	0.26 (0.16-0.42)	<0.0001
Brain metastasis	0.42 (1.18-2.75)	0.009	0.52 (1.01-2.59)	0.044

HR, hazard ratio; CI, confidence interval.

Table IV. Adverse events.

Adverse event	All grades (n)	%
Dermatitis	25	10
Colitis	9	3.6
Hypothyroidism	7	2.8
Hypophysitis	5	2
Pneumonitis	4	1.6
Other adverse events	5	2

PR, 80 months in those with stable disease, and 34 months in those with disease progression. The difference between the survival curves was statistically significant (Fig. 6).

Multivariate analysis revealed that there was no statistically significant difference in median OS based on age. However, differences in median OS were statistically significant based on presence of objective response, *de novo* metastasis, and brain metastasis (respectively, P values: P<0.0001, P<0.0001 and P=0.044) (Table III). Therefore, it was revealed that the absence of objective response, presence of *de novo* metastasis, and presence of brain metastasis are independent poor prognostic factors affecting survival.

Toxicity. Some degree of immune-related adverse events was observed in 55 patients (22%), whereas grade 3 and 4 immune-related adverse events were observed in 18 patients (7.2%). The most common adverse events were dermatitis (10%), colitis (3.6%), (and hypothyroidism (2.8%). There were no deaths due to adverse events. A total of seven patients (2.8%) discontinued treatment due to adverse events. Adverse events were generally manageable, and the vast majority responded to corticosteroid therapy. Safety data is summarized in Table IV.

Discussion

ICIs have markedly changed the standard treatment of advanced-stage melanoma. The effectiveness of these drugs was reported in numerous studies (4-6). The present study aims to examine the real-life data of Turkish patients with metastatic melanoma treated with ICIs. The present study included patients who were not included in clinical trials, and the effectiveness and reliability of ICIs were investigated in these patients. Among these patients, there were those with poor prognoses, such as elderly patients and patients with brain metastases. A total of 22% of the patients were >70 years of age, and 26% had brain metastases. Including patients with poor prognoses, the present study was an important study that presented real-life data on the treatment of metastatic melanoma with ICIs.

Abali *et al* (7) analysed 1,157 patients diagnosed with melanoma in a retrospective study conducted as a project of the Turkish Oncology Group, which is a pioneer in the field of melanoma in Turkey. The patients in that study presented with more advanced stages and they had worse prognosis compared with SEER database.

There are a limited number of studies investigating real-world data ICI therapy in patients with metastatic melanoma outside of clinical trials. In one of these studies, Urun *et al* (8) in 2019 investigated prognostic factors in 97 patients with metastatic melanoma treated with Ipilimumab in Turkey. In the aforementioned retrospective study presenting real-world data, the median OS was found to be 9.7 months. In addition, as a result of multivariate analysis, RECIST response (CR or partial PR), absolute lymphocytes count (>1,500/mm^3) and the number of metastatic sites (<3 sites) were found as significant independent prognostic factors for longer survival. In another study conducted in Korea, the PFS in patients with metastatic melanoma receiving Ipilimumab therapy was found to be 2.7 months. The aforementioned study included 104 patients, among whom there were cases of uveal and mucosal melanoma, while only 26% of the patients had cutaneous melanoma. Therefore, the lower efficacy observed compared with other studies was attributed to this patient distribution (9).

Parakh *et al* (10) examined real-world data on the efficacy of combined Ipilimumab and Nivolumab therapy in patients with metastatic melanoma in Australia. In the aforementioned study, which included 45 patients the ORR was 29%. The median PFS was 5.8 months, and the median OS was 17.4 months. The rate of grade 3-4 adverse events was 54%. This study's high incidence of adverse effects was due to the patients receiving combination therapy. In another study conducted by Asher *et al* (11), real-world data from 172 patients

in Israel who received Ipilimumab and Nivolumab therapy for metastatic melanoma were analysed. The ORR was 61%. The median PFS was 12.2 months, while the median OS was not reached. The rate of grade 3-4 adverse events was 59%. The higher efficacy observed in the aforementioned study compared with the present was due to the most patients received combination therapy as a first-line treatment. Recently, in a study conducted by Staeger *et al* in 2024, which examined real-life data, the 5-year survival rate in patients diagnosed with metastatic melanoma who received anti-PD1 therapy was found to be 46.5% and in those who received anti-CTLA4/PD1 combination therapy, it was found to be 52.4%. The study also demonstrated that patients with brain metastases and elevated serum LDH levels had a worse prognosis (12).

In the aforementioned study, the ORR was found to be 37.7% in patients with metastatic melanoma receiving ICI therapy. According to the 5-year follow-up results of the CheckMate 066 study, the ORR was 42% in patients with metastatic melanoma who received Nivolumab as primary therapy (5). According to the 5-year follow-up results of the KEYNOTE-006 study, the ORR was 46% in patients with metastatic melanoma who received Pembrolizumab as first-line therapy (4). In Turkey, the coverage of ICI treatment for metastatic melanoma under the state-provided general health insurance is after chemotherapy as second-line therapy. Therefore, the majority of patients had received ICI treatment as second-line therapy (21% of patients received ICI treatment as first-line therapy, while 79% received it as second-line therapy). The administration of ICIs as first-line therapy was found to be more effective than as second-line therapy. In the KEYNOTE-006 study, the ORR was 46% in patients who received Pembrolizumab as first-line therapy, while it was 34% in patients who received Pembrolizumab as second-line therapy (4). Therefore, in the present study, the ORR was lower than other studies where ICIs were administered as first-line therapy. Additionally, in the present study, none of the patients treated with ICIs had received Pembrolizumab. This is because the coverage of Nivolumab treatment for metastatic melanoma under the state-provided general health insurance is covered by the state in Turkey, but Pembrolizumab treatment expenses are not covered.

In the present study, the median OS for all patients was 61 months. When stratified by the ICI agent given to the patient, the median OS was 77 months in patients who received Nivolumab, 46 months in patients who received Ipilimumab, and 42 months in patients who received Ipilimumab + Nivolumab. In the KEYNOTE-006 study, the median OS was 33 months for those receiving the Pembrolizumab and 16 months for those receiving the Ipilimumab (4). According to the 6.5-year follow-up results of the CheckMate 067 study, the median OS was ~72 months in the Ipilimumab + Nivolumab combination, 37 months in the Nivolumab, and 20 months in the Ipilimumab (6). In the present study, the median OS was longer in patients treated with Nivolumab compared with other studies, which was a notable result of the study. In the present study, the longer survival duration compared with clinical trials may be due to the fact that people living in the Middle East region, where Turkey is located, have a different genetic structure than those living in Europe and America. As an example of this, in a study conducted by Asher *et al* (11) from Israel, the median OS had not yet been reached in patients receiving combination therapy with Ipilimumab and Nivolumab for metastatic melanoma, and this survival duration was longer compared with other clinical trials. However, in patients receiving Ipilimumab + Nivolumab combination therapy, the median OS was shorter when compared with other studies. This was because there were only 2 patients in this group, and therefore, no reliable result could be obtained from this small number of patients.

In the present study, the multivariate survival analysis revealed that the absence of an objective response, the presence of *de novo* metastasis, and the presence of brain metastasis were poor prognostic factors that negatively affected survival independently of other factors. Currently, patients with brain metastasis are not included in most clinical trials. Studies showing real-life data including patients with brain metastasis are limited. In a study by Jung *et al* (9) demonstrating real-life data on Ipilimumab, while brain metastasis was found as a poor prognostic factor in univariate analysis, this could not be demonstrated in multivariate analysis.

Regarding side effects, in the present study where the majority of patients received Nivolumab, grade 3-4 immune-related side effects were observed in 7.2% of patients and 2.8% of patients discontinued treatment due to side effects. In the CheckMate 066 study, the rate of grade 3-4 side effects in patients receiving Nivolumab was 16%, while in the CheckMate 067 study, the rate of grade 3-4 side effects in patients receiving Nivolumab was 22% (5,6). Fewer side effects were observed in the patients in the present study compared with other studies, which is another noteworthy result of the study.

The most important limitations of the present study are its retrospective nature, the small number of patients included, and the fact that multiple patients received immunotherapy as second-line therapy, and none of the patients received Pembrolizumab due to the conditions in our country.

In conclusion, the present study is important as it examines real-life data of patients with metastatic melanoma receiving ICI treatment in Turkey and therefore reveals different prognostic factors; therefore, it is considered to make a significant contribution to the literature.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AO conceptualized, designed, received ethics approval, and initiated the present study. AO, FM, ID, SV, ME, AE, GO, MA,

MT, MY, EH, OB, BT, AD, AC, SS, GC, HD, OD, MG, EC, IH, AG, OU, PP, TS, AG, HH, EE, ET, OE, SL, OK, PO, ST, KO and BY collected data for the study. AO wrote the original article, made the statistics, prepared the tables and figures. BY revised the original article and finalized it together with AO. AO and BY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present multicenter retrospective study was approved by the Ethics Committee of the University of Health Sciences (approval no. 05.04.2021-25877; Istanbul, Turkey).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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