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Indirect comparison of treating patients with advanced/metastatic melanoma with nivolumab or pembrolizumab — multicenter analysis

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ABSTRACT

Introduction. The development of a new class of drug — checkpoint inhibitors has changed the prognosis of cancer patients. A particular class of drugs are antibodies against the programmed cell death type 1 receptor/ligand of the programmed cell death type 1 receptor (nivolumab and pembrolizumab). There are, however, no trials with a random selection of the patients which directly compare nivolumab and pembrolizumab. Because of the development of immunotherapy and many new drugs registered as anti-PD-1, it is important to determine whether there are differences in respect to effectiveness and safety in using nivolumab and pembrolizumab.

Material and method. 499 patients with non-resectable or metastatic melanoma treated in the years 2016–2019 in five oncological reference centers in Poland (Cracow, Gliwice, Lublin, Poznań, Wrocław) were included in the analysis. The criterion for inclusion in the analysis was first-line treatment with anti-PD-1 (nivolumab or pembrolizumab).

Results. Median OS and PFS in the whole analyzed group were 19.9 and 7.9 months, respectively. Estimated median OS and PFS were 20.1 and 18.1 months and 8.5 and 6.0 months for nivolumab and pembrolizumab, respectively. No statistically significant difference was observed in median OS and PFS in the group of patients receiving nivolumab and pembrolizumab (respectively P = 0.6291 [HR = 1.06; CI 95% 0.8–1.4] and P = 0.0956 [HR = 1.20; CI 95% 0.97–1.48]). The percentage of grade G3 or/and G4 irAEs was similar in both groups treated with nivolumab or pembrolizumab, 5.8 and 5.2%, respectively.

Conclusions: No differences in the range of OS, PFS and ORR was observed between therapy with nivolumab and pembrolizumab in previously untreated patients with advanced/metastatic melanoma. No differences were found in the frequency of irAEs of grade G3 or G4. The treatment with a specific preparation should be based on the preferences of the patient and the clinician.

Key words: melanoma, immunotherapy, antiPD-1 therapy, pembrolizumab, nivolumab

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Introduction

In recent years the treatment of patients with diagnosed melanoma has changed greatly due to the development of a new class of drugs: antibodies against the programmed cell death type 1 receptor/ligand of the programmed cell death type 1 receptor (anti-PD-1/anti-PD-L1, anti-programmed death receptor-1/ligand-1). The mechanism of action of anti-PD-1 antibodies, which include nivolumab and pembrolizumab, is based on binding of the drug to the PD-1 receptor and blocking interactions with the PD-L1 and PD-L2 ligands, which in turn activates T lymphocytes to an immunological response against neoplastic cells [1–3]. Nivolumab has the structure of a human monoclonal IgG4 antibody with a half-life of about 26 days and shows specificity for the PD-1 receptor [2]. Pembrolizumab is a humanized monoclonal IgG4 antibody with a half-life of about 27 days [3]. Another difference is the dosing of the two drugs. Nivolumab is currently used at a constant dose of 240 mg every 2 weeks or 480 mg every 4 weeks, whereas pembrolizumab is given in a dose of 200 mg every 3 weeks or 400 mg every 6 weeks [4]. The comparison (indirect) of the results of trials with randomization in patients with melanoma treated with nivolumab or pembrolizumab indicates similar effectiveness of both these drugs. However, in patients with metastatic non-small cell lung carcinoma (NSCLC) differences in the effectiveness of nivolumab and pembrolizumab depending on PD-L1 expression were observed [5, 6], which could suggest some differences in the action of the two drugs. There are, however, no trials with a randomized selection of patients which directly compare nivolumab and pembrolizumab. Because of the development of immunotherapy and many new registrations for anti-PD-1 drugs, it is important to determine whether there are differences in the range of effectiveness and safety in using nivolumab and pembrolizumab.

According to the best knowledge of the authors, this is the first and largest analysis comparing the effectiveness and toxicity of nivolumab and pembrolizumab in everyday practice.

Material and method

499 patients with non-resectable or metastatic melanoma treated in the years 2016–2019 in five oncological reference centers in Poland (Cracow, Gliwice, Lublin, Poznań, Wrocław) were included in the analysis. The criterion for inclusion in the analysis was first-line treatment with anti-PD-1 (nivolumab or pembrolizumab). All patients were treated according to the indications of the national drug program: treating skin or mucous membrane melanoma. A detailed description in Polish is available on https://www.gov.pl/web/zdrowie/choroby-onkologiczne [7]. All patients received nivolumab or pembrolizumab, in doses in agreement with the drug characteristics currently in force and the guidelines of the drug program. In all analyzed patients data were collected on age, sex, localization of the primary lesion, degree of disease progression according to TNM (AJCC 8th edition), localization and number of metastases, level of lactate dehydrogenase (LDH), ECOG (Eastern Cooperative Oncology Group) performance status and type of therapy used in first-line and second-line treatment. Information on the degree of disease progression, localization and number of metastases, level of lactate dehydrogenase (LDH) and ECOG performance status [8] were collected at the moment of initiating first-ine systemic treatment. No data on PD-L1 expression were collected as the assays were not available. All patients were treated until disease progression, unacceptable therapy toxicity, death or withdrawal of consent for treatment. The first radiological evaluation was performed after 12 weeks from initiating anti-PD-1 therapy, and then the radiological evaluations of the patients were performed every 3 months according to the requirements of the drug program. Evaluation of the response to treatment was performed according to z RECIST 1.1 criteria [9], according to the requirements of the National Melanoma Treatment Program [7]. Data on the safety of the applied treatment were also collected.

Statistical analysis

The statistical analysis encompassed comparison of nivolumab and pembrolizumab therapy. Endpoints encompassed the comparison of median time to disease progression (PFS, progression-free survival), overall survival (OS) and evaluation of indices of objective response to therapy (ORR, overall response rate) and disease control rate (DCR) defined by the RECIST 1.1. criteria. PFS or OS were evaluated from the beginning of nivolumab or pembrolizumab therapy until disease progression according to RECIST, death or last documented contact. The Kaplan-Meier method was used for estimating PFS and OS with a 95% confidence interval (CI), and the survival curves were analyzed using log-rank. To determine in the multivariate model the significance of the effects of the prognostic variables on PFS and OS at the moment of initiation of anti-PD-1 therapy the Cox proportional hazard model was used. Differences were considered to be statistically significant if the P value was < 0.05. All statistical analyses were performed using STATISTICA 12.

Results

General characteristics of the analyzed group

In the group of 499 patients receiving anti-PD-1 therapy 308 (62%), patients received nivolumab and 191 (38%) pembrolizumab. No statistically signifi-

Table 1. Characteristics of the analyzed group

Variable	Category	Nivolumab n = 308	Pembrolizumab n = 191	P-value
Age (years)	Median (range)	66 (23–93)	68 (27–92)	
	< 65 years	132 (43%)	76 (40%)	0.5
Gender	Male	184 (60%)	111 (58%)	0.72
	Female	124 (40%)	80 (42%)	
BRAF mutation	No mutation	244 (80%)	156 (83%)	0.34
	Mutated	61 (20%)	31 (17%)	
Location of the primary tumor	Skin	272 (89%)	175 (92%)	0.34
	Mucosal	20 (7%)	10 (5%)	
	Unknown	13 (4%)	5 (3%)	
ECOG	0	117 (38%)	77 (40%)	0.57
	1	188 (61%)	111 (58%)	
	2	3 (1%)	2 (2%)	
LDH level	Normal	189 (62%)	108 (56%)	0.43
	> normal	118 (38%)	82 (44%)	
Brain metastasis	No	257 (83%)	155 (81%)	0.51
	Yes	51 (17%)	36 (19%)	
TNM stage (AJCC 8th edition)	III	22 (7%)	6 (3%)	0.25
	M1a	62 (20%)	33 (17%)	
	M1b	65 (21%)	38 (20%)	
	M1c	108 (35%)	78 (41%)	
	M1d	51 (17%)	36 (19%)	
Number of metastatic sites	< 2	85 (28%)	49 (26%)	0.63
	≥ 2	223 (72%)	142 (74%)	

AJCC — American Joint Committee on Cancer; ECOG — Eastern Cooperative Oncology Group; LDH — lactate dehydrogenase; TNM — tumor, node, metastasis

cant differences between the two groups were found in the general characteristics of patients. In the group receiving pembrolizumab there were slightly more patients with metastases to the brain (19% *vs.* 17%) and elevated LDH levels (44% *vs*. 38%) A detailed characterization of the analyzed groups is presented in Table 1.

Treatment results depending on the used therapy

Estimated median OS and PFS in the whole analyzed group were 19.9 and 7.9 months, respectively. Estimated median OS was 20.1 and 18.1 months for nivolumab and pembrolizumab, respectively. No statistically significant difference in median OS was observed between the groups of patients receiving nivolumab and pembrolizumab (P = 0.6291, HR = 1.06; Cl 95% 0.8–1.4) (Fig. 1). The estimated median PFS was 8.5 and 6.0 months for nivolumab and pembrolizumab, respectively and no statistically significant difference in median PFS was found between the groups of patients receiving nivolumab and pembrolizumab (P = 0.0956, HR = 1.20; Cl 95% 0.97–1.48) (Fig. 2). 1-, 2- and 3-year survivals were similar in both groups. No differences were observed in responses to treatment. Detailed data on the results of treatment are presented in Table 2.

Adverse effects

A slightly higher percentage of patients with immunological complications (irAE) were noted in the group of patients receiving nivolumab (25% *vs.* 21.6%). However, the percentage of grade 3 and/or 4 irAEs was similar in both groups treated with nivolumab or pembrolizumab, 5.8 and 5.2%, respectively. In the group receiving pembrolizumab skin, hematological and kidney complications were more common. In the group with nivolumab liver, lung and neurological complications were more common. Endocrinological complications concerning thyroid function were different in both groups of patients. In the group receiving nivolumab, there was more hyperthyroidism, but in 60% (12 patients) of cases, the hyperthyroidism changed into hypothyroidism. In the group receiving pembrolizumab one serious G3 complication related to the drug was observed. No irAE related death was observed in either of the groups. The irAEs are presented in detail in Table 3.

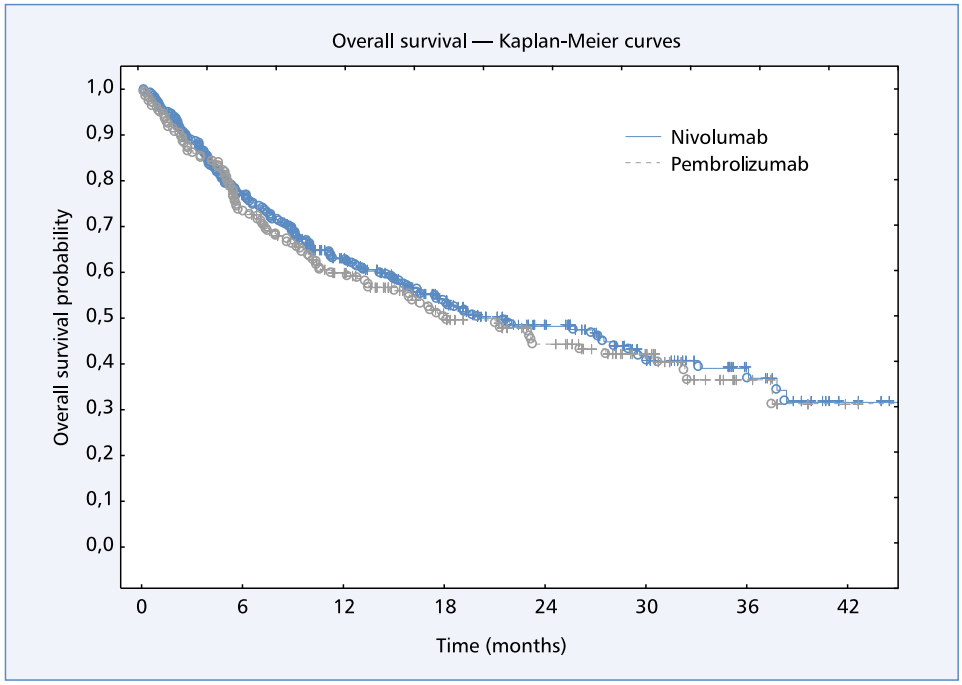

Figure 1. Overall survival depending on the used anti-PD-1 therapy

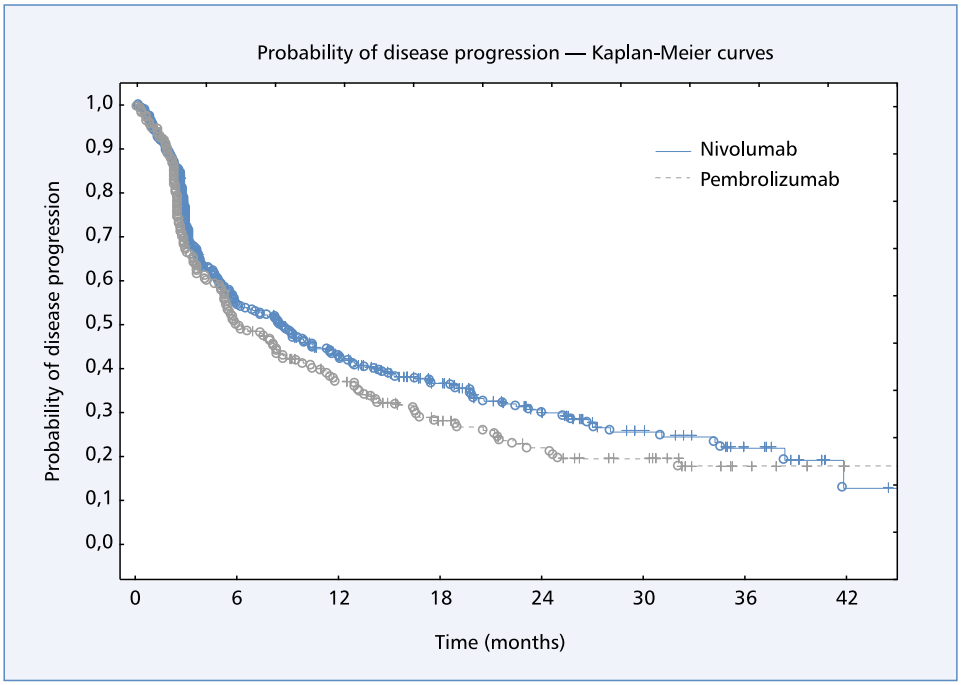

Figure 2. Time to disease progression depending on the anti-PD-1 therapy used

Discussion

In the presented retrospective analysis encompassing treatment results in everyday medical practice (real-world data), no differences were observed in OS and PFS, nor in responses to treatment between nivolumab and pembrolizumab therapy. Also in the analysis by Moser et al., where the results were compared in everyday medical practice of 486 patients treated with pembrolizumab and 402 treated with nivolumab no differences in OS were found between nivolumab and pembrolizumab [10]. Median OS in the whole analyzed

Table 2. Effectiveness of therapy depending on the used drug

Factors		Nivolumab n = 308	Pembrolizumab n = 191
Median OS (months)		20.1	18.1
Estimated overall survival	1 year OS	62%	59%
	2 years OS	48%	44%
	3 years OS	36%	36%
Median PFS (months)		8.5	6.0
Best overall tumor response	CR	6%	5%
	PR	27%	31%
	SD	30%	27%
	PD	37%	37%
	ORR (CR+PR)	33%	36%
	DCR (CR+PR+SD)	63%	63%
Duration of treatment	Median (range) months	6.3 (0.1–41)	5.1 (0.1–43)
irAEs	Patients with irAEs	77 (25%)	41 (21.5%)
The next line of treatment	All	111 (36%)	75 (39%)
	Immunotherapy	80 (72%)	58 (77%)
	Targeted therapy	19 (17%)	12 (16%)
	Chemotherapy	11 (10%)	5 (7%)
	Other	1 (1%)	0

CR — complete response; DCR — disease control rate; irAEs — immune related adverse events; NE — not evaluated; OS — overall survival; ORR — objective response rate; PD — progression disease; PFS — progression free survival; PR — partial response; SD — stable disease

Table 3. Immunological complications during anti-PD-1 therapy

	Nivolumab, n = 308		Pembrolizumab, n = 191	
irAEs	**All grade, n (%)**	**G3 or G4, n (%)**	**All grade, n (%)**	**G3 or G4, n (%)**
Patients with irAEs	77 (25%)		41 (21.5%)	
Overall irAEs	121 (39%)	18 (5.8%)	63 (33%)	10 (5.2%)
Dermatitis (rash)	8 (2.6%)	1 (0.3%)	10 (5.2%)	2 (1%)
Vitiligo	3 (1%)	0	3 (1.6%)	0
Diarrhea/colitis	8 (2.6%)	3 (1%)	4 (2.1%)	1 (0.5%)
Hepatitis or AST/ALT elevation	29 (9.4%)	9 (3%)	10 (5.2%)	2 (1%)
Hypothyroidism	24 (7.8%)	0	16 (8.4%)	0
Hyperthyroidism	21 (6.8%)	0	1 (0.5%)	0
Hypopituitarism/hypophysitis	1 (0.3%)	0	0	0
Pneumonitis	8 (2.6%)	1 (0.3%)	1 (0.5%)	0
Neurological/neuropathy	1 (0.3%)	1 (0.3%)	0	0
Hematological (neutropenia, anemia)	0	0	5 (2.6%)	3 (1.6%)
Cardiological	2 (0.6%)	0	1 (0.5%)	0
Arthralgia/myalgia	3 (1%)	0	2 (1%)	0
Nephritis	2 (0.6%)	0	3 (1.6%)	0
Other	11 (3.6%)	4 (1.3%)	7 (3.7%)	2 (1%)

ALT — alanine aminotransferase; AST — aspartate aminotransferase; irAEs — immune related adverse events

group was 19.9 months and was similar to the median OS in the analysis by Moser et al. [10] (22.6 months). Median OS in both analyses is shorter than in clinical trials for nivolumab and pembrolizumab, 37.5 and 32.7 months, respectively [11–14]. This is probably due to the fact that in our trial almost 20% of patients has metastases to the central nervous system (CNS), which is a known poor prognostic factor. In the Checkmate-066 trial patients with metastases to the brain constituted only 3.6% and in the Keynote-006 trial 9% [11–14]. It should also be noted that the criteria for inclusion in drug programs require additional examinations in patients with metastases to the CNS, which significantly delays the initiation of anti-PD-1 therapy.

In our analysis, PFS and response to treatment were also evaluated, which was not done in the work of Moser et al. because of the lack of data. Median PFS and the number of responses were close to those presented in clinical trials of nivolumab (Checkmate-066) and pembrolizumab (Keynote-006), in which they were 5.1 and 8.4 months, respectively, and the number of objective responses (ORR) 40 and 33–34%, respectively [11, 12].

One of the more important aspects of our analysis is the analysis of immunological toxicity of nivolumab and pembrolizumab therapy. The number of irAEs is smaller than in clinical trials, which may be due to the retrospective character of the presented results and the lack of reporting of especially grade 1 irAEs in everyday clinical practice. It should be also pointed out that in our trial there are slightly fewer G3 and G4 adverse effects than in clinical trials. No irAE related deaths were observed. This may be related to the increasingly common use of anti-PD-1 in clinical practice and thus better management of immunological toxicities, the so-called learning curve. However, the number of grade G3 and G4 irAEs was similar in the group with nivolumab and with pembrolizumab. However, it should be observed that nivolumab and pembrolizumab have a slightly different toxicity profile — irAEs. This is particularly clear in thyroid-associated endocrinological perturbations. It is not clear why hyperthyroidism, which in most cases became hypothyroidism was more frequent in the nivolumab group. This could be linked to the size of both analyzed groups (the group with nivolumab was much larger). Further observations and trials are certainly necessary.

Conclusions

No differences were observed in OS, PFS and ORR between nivolumab and pembrolizumab treatment in previously untreated patients with advanced/metastatic melanoma. No differences were observed in the frequency of grade G3 or G4 irAEs. The choice of treatment with a specific preparation should be based on the preferences of the patient and the clinician.

Conflict of interest

PR — honoraria from BMS, MSD, Novartis, Amgen, Pierre Fabre, Sanofi, Merck and Blueprint Medicines for lectures and Advisory Boards outside of the scope of the study. JM — grants and consultancies — BMS, MSD. Fees and honoraria: AMC, TK, JC — Bristol-Myers Squibb, Novartis, Roche, Merck; BCS — BMS, Novartis, Roche, Pierre Fabre, MSD; RS — BMS, MSD, Astellas Pharma; JM — BMS, GlaxoSmithKline, Roche, MSD, Novartis, Pierre Fabre.

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