VIA MEDICA

ORIGINAL ARTICLE

Paweł Rogala[1], Joanna Stępniak[1], Tomasz Świtaj[1], Ewa Kalinka-Warzocha[2], Katarzyna Kozak[1], Hanna Koseła-Paterczyk[1], Piotr Rutkowski[1]

[1]Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie, Warszawa
[2]Oddział Chemioterapii, Wojewódzki Szpital Specjalistyczny, Łódź

The activity of pembrolizumab in therapy of pretreated metastatic melanomas — two centres' experience

Primary results of the study were presented at the Congress of the Polish Oncology Society in the year 2016

Address for correspondence:
Lek. Paweł Rogala
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie
ul. Roentgena 5, 02–781 Warszawa
Phone: +48 (22) 546 20 31
e-mail: progala@coi.waw.pl

Oncology in Clinical Practice
2016, Vol. 12, No. 5, 161–166
DOI: 10.5603/OCP.2016.0008
Translation:
dr n. med. Hanna Koseła-Paterczyk

ISSN 2450–1654

ABSTRACT

Introduction. Pembrolizumab [programmed death 1 (PD-1) checkpoint inhibitor] mediates durable responses and prolongs survival in patients with advanced melanomas. We assessed the efficacy and safety of pembrolizumab in pretreated metastatic melanoma patients outside clinical trials.

Methods. Fifty-four patients (median age 57 years; range 18–77) after progression on previous therapy (at least ipilimumab) in metastatic setting were administered pembrolizumab at a registered dose 2 mg/kg every three weeks and were observed for progression-free survival (PFS), overall survival (OS), responses, and toxicity. Median follow-up time for survivors was 8.5 months.

Results. In all except six cases pembrolizumab was given in at least third line of systemic therapy. All patients (except two patients with ocular melanomas) had cutaneous origin of the primary; 16 were *BRAF*-positive (30%), 42 patients were in M1c stage (78%); and 27 patients had increased initial LDH level (50%). The clinical benefit of pembrolizumab therapy was 50% with one complete remission, seven partial remissions, and 19 stable diseases. Thirty-six patients received more than four doses of the drug; 13 patients still remain on treatment. Median OS was not reached. The estimated one-year OS was 48%. We observed no differences in OS between *BRAF*-positive and *BRAF*-negative cases. Poorer OS was found in patients with initially increased LDH level ($p = 0.04$), and slightly worse results were seen for patients treated with more than three lines of therapy and in M1c stage. Median PFS was 5.6 months, estimated one-year PFS rate was 40%, and better PFS was observed for patients with initially normal LDH (7.5 *vs*. 4.5 months; $p = 0.02$). The treatment was well tolerated with adverse events (AE) occurring in 14 patients (26%), but in only three cases grade 3 AEs were observed (6%): diarrhoea, diabetes mellitus, pneumonitis.

Conclusions. Pembrolizumab confirmed its activity and safety outside clinical trials in therapy of pretreated metastatic melanomas. Anti-PD-1 inhibitors are the preferred treatment option in advanced melanoma management.

Key words: pembrolizumab, anti-PD-1 inhibitors

Oncol Clin Pract 2016; 12, 5: 161–166

Introduction

The treatment of patients with metastatic melanoma is still a challenge for medical oncologists. Five years ago in Poland the only widely available treatment option was chemotherapy, which in this group of patients gave a median survival time of between six and nine months. Anti-PD-1 antibodies (PD-1 — programmed cell death protein-1) belong to a group of drugs that have significantly changed the treatment outcomes [1].

In September 2014, the first representative of this class of drugs, nivolumab, was approved by the Food and Drug Administration (FDA) for use in patients with advanced melanoma; in December of the same year pembrolizumab was registered in the foregoing diagnosis. The European Medicines Agency (EMA) approved two drugs in July 2015. These dates have a specific impact on the length of the extended access program to pembrolizumab. In Poland, the program lasted from March to July 2015 — recruitment was completed at the time of approval of the drug by the EMA. During this period of less than four months we had the opportunity to include dozens of patients into the program. Some of the patients were still on therapy. In this work we would like to present the experiences of two cancer centres in the use of pembrolizumab, one of two available monoclonal anti-PD-1 antibodies.

Methods

Within the expanded access program (EAP) in the Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw and in Nicolaus Copernicus University Hospital in Lodz since March 2015 a total of 54 patients were treated (mean age 57 years, range 18–77) — 47 in Warsaw and 7 in Lodz. The main inclusion criterion in the program was the diagnosis of unresectable or metastatic melanoma after progression on ipilimumab treatment. Other inclusion criteria were: Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and adequate function of the liver, kidneys, and bone marrow. Exclusion criteria were limited to: clinically significant autoimmune diseases, active metastatic lesions in central nervous system infections, HCV, HBV, or HIV infection. It was agreed that the duration of participation in the program would be up to two years.

Patients received pembrolizumab in the registered dose of 2 mg/kg every three weeks. They were monitored for progression-free survival (PFS, counted from the start of pembrolizumab treatment until progression, death, or last follow-up), overall survival (OS, counted from the start of pembrolizumab treatment until death or last observation), response to treatment (according to RECIST criteria 1.1, the first response assessment was performed using computed tomography after 12 weeks of treatment), and adverse events. Data concerning tolerance of therapy was assessed in accordance with the fourth version of Common Terminology Criteria for Adverse Events (CTCAE). For survival analysis the Kaplan-Meier method was used, and log-rank test was used for two-way analysis. Statistical analysis was performed using Statistica 7.1. Median time of follow-up was 8.5 months.

Table 1. Characteristics of patients (n = 54)

Sex	
Women	22 (41%)
Men	32 (59%)
Age	
Average	57
Range	18–77
Cutaneous melanoma	52 (96%)
Ocular melanoma	2 (4%)
BRAF mutation	
Present	16 (30%)
Absent	38 (70%)
The advancement of the disease	
M1a	6 (11%)
M1b	6 (11%)
M1c	42 (78%)
LDH level	
Normal	27 (50%)
Elevated	27 (50%)

Results

Characteristics of the patients treated with pembrolizumab are shown in Table 1. Forty-eight patients received pembrolizumab as at least the third line of treatment of metastatic disease (89%). In six patients pembrolizumab was used as the second line of systemic therapy (11%). One patient received the drug in the sixth line of treatment.

With the exception of two cases of ocular melanoma, patients were diagnosed with cutaneous melanoma. *BRAF* mutation was detected in 16 patients (30%); the remaining 38 patients had no *BRAF* mutations (70%). Patients with *BRAF* mutation before pembrolizumab therapy received prior treatment with BRAF inhibitors. Six patients were in stage M1a (metastases to the skin, subcutaneous tissue, or non-regional lymph node) (11%), six in stage M1b (lung metastases) (11%), and 42 patients were in stage M1c of the disease (other sites of metastases or increased activity lactate dehydrogenase — LDH) (78%); 27 patients had an increased LDH level at the onset of pembrolizumab therapy (50%).

Clinical benefit from treatment with pembrolizumab was found in 50% of patients, with one complete remission (CR) (2%), seven partial remissions (PR) (13%), and 19 stable disease (SD) (35%) lasting more than four months. The patient who obtained complete remission completed treatment within the extended access program, remains under observation, and is still free of the disease. During two years of treatment (he began

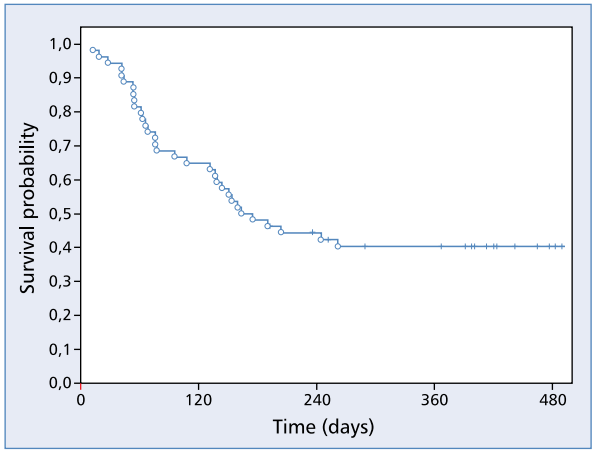

Figure 1. Progression-free survival

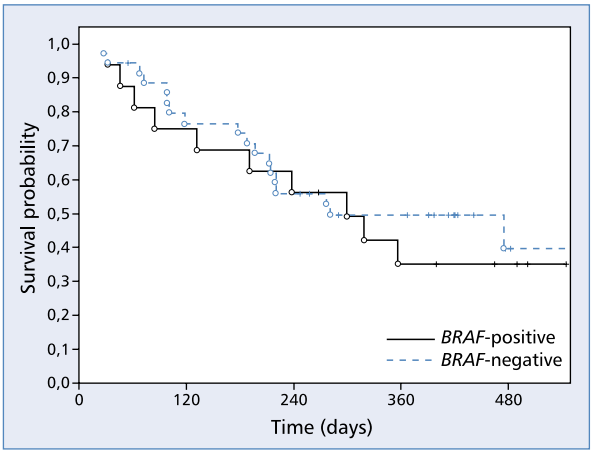

Figure 3. Overall survival of the patients treated with pembrolizumab, depending on the status of *BRAF* mutation

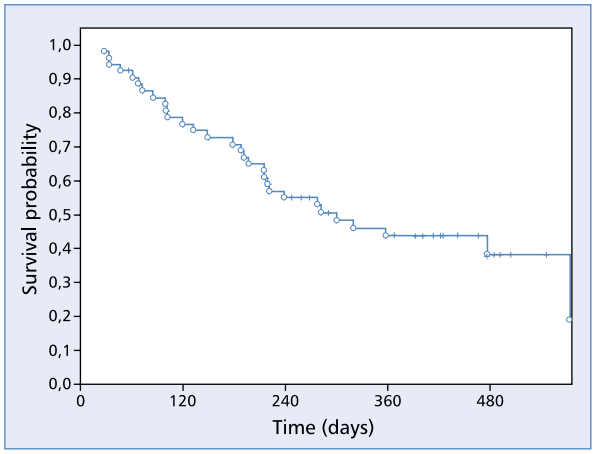

Figure 2. Overall survival

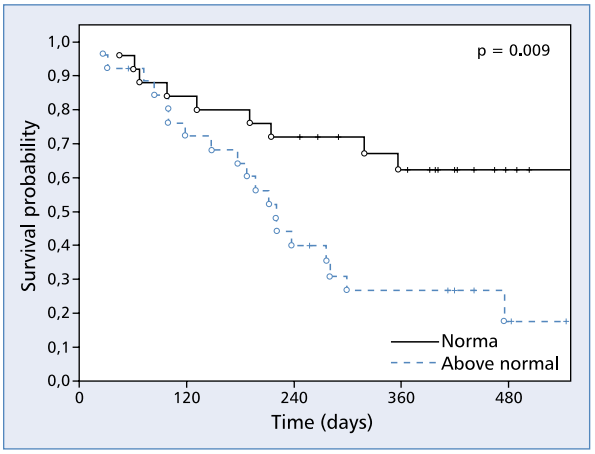

Figure 4. Overall survival of patients, depending on the activity of LDH at the onset of pembrolizumab treatment

therapy abroad) the patient received a total of 39 doses of pembrolizumab.

Thirty-six patients received at least four drug doses, 13 patients are still on therapy. The median PFS was 5.6 months, with an estimated one-year PFS of 40% (Fig. 1); longer PFS was observed in patients with normal LDH level (7.5 *vs.* 4.5 months; $p = 0.02$). The median OS was not reached, and the estimated percentage on one-year overall survival was 48% (Fig. 2). We did not observe any differences in OS between *BRAF*-positive and *BRAF*-negative patients (Fig. 3), and poorer survival was observed in patients with increased LDH ($p = 0.009$) (Fig. 4); slightly inferior results were observed in the group of patients treated at more than three lines of therapy ($p < 0.05$), and in stage M1c ($p < 0.05$).

In three cases we decided to use concurrent radiotherapy during pembrolizumab treatment. In one patient metastatic lesions to the oesophagus were irradiated, the second patient had stereotactic radiotherapy for metastases in the area of the brain, and the third patient received irradiation to the lesions in the right adrenal gland. We did not observe any adverse effects associated with concomitant radiotherapy and immunotherapy.

Patients were evaluated for the occurrence of adverse events, in particular the adverse effects associated with the immune system. Adverse reactions associated with pembrolizumab occurred in 14 patients (26%). The most frequent was diarrhoea — in four patients (7%) — of which two experienced the adverse event in stage 1, one in grade 2, and one in grade 3. Other side effects included: skin rash grade 1 CTCAE version 4 — two patients (4%) and grade 2 — two patients (4%); fatigue grade 1 occurred in three patients (6%); and bone and joint pain grade 1 in two patients (4%). Single cases of fever, and abnormal levels of TSH, and fT3 and fT4 hormones also occurred. Chills, pain of metastatic lesions to the skin, diabetes mellitus, and pneumonia were also reported. Besides diabetes mellitus and pneumonia, the

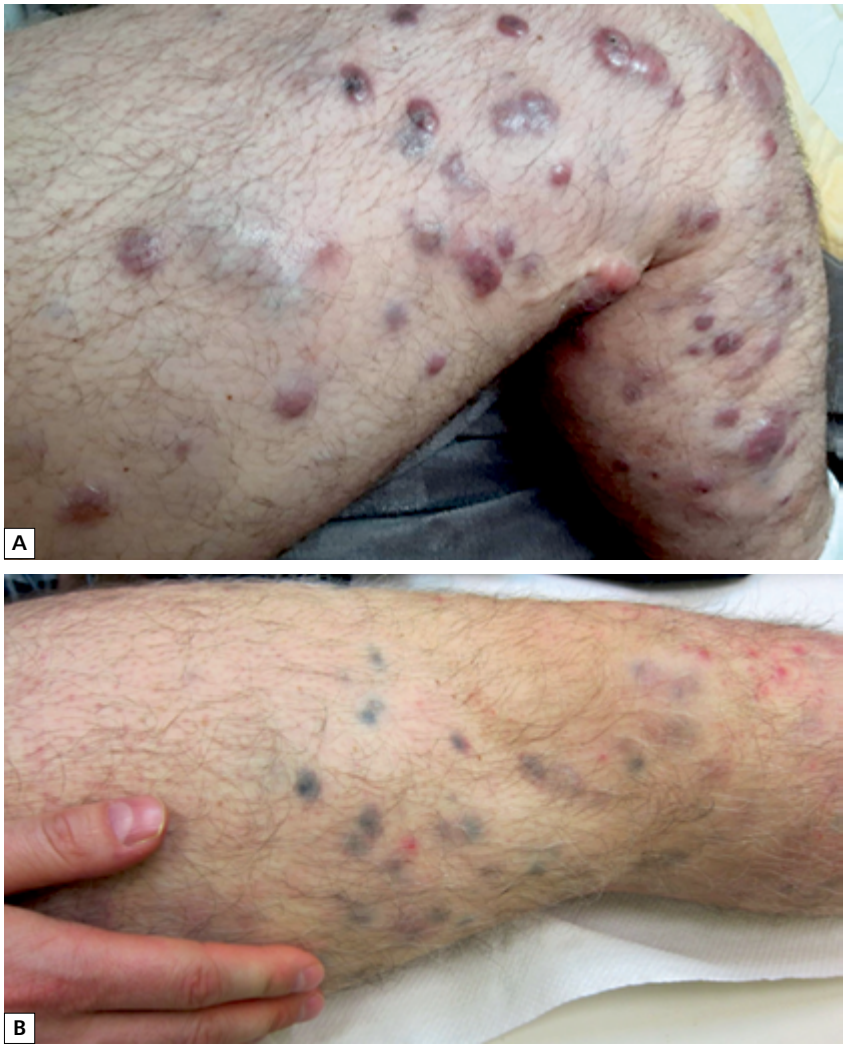

Figure 5. Pictures of the partial remission of in-transit lesions of metastatic melanoma to the lower limb during pembrolizumab treatment. **A.** Before treatment; **B.** After 3 months of therapy

severity of which was determined as grade 3, the other listed occurred in grade 1. In total grade 3 side effects were reported in three patients (6%). Pneumonia and diarrhoea grade 3 were the reason for stopping treatment with pembrolizumab. Diabetes, which occurred in a patient with ocular melanoma, was easily controlled by insulin therapy and was not the reason for discontinuation of the program.

Discussion

Immune checkpoint inhibitors blocking PD-1/PD-L1 represent a third type of modern armamentarium for the systemic treatment of cancer, next to chemotherapy and targeted therapy. They have a unique mechanism of action by enhancing or stimulating de novo antitumor response of the immune system in order to eliminate cancer. Existing data for two of these agents — pembrolizumab and nivolumab — indicate similar activity, much higher than those achieved with previous generation immunotherapy with anti-CTLA-4 antibodies (because their effect on the immune system occurs at a deeper effector stage) with a median survival in the first line exceeding two years. Moreover, these new drugs have a better safety profile [2, 3].

In the group analysed by us, eight patients achieved treatment response (CR and 1 PR 7) (Fig. 5). Response to treatment was assessed by RECIST 1.1. The objective response rate was thus 15% (8/54). It is lower than the percentage reported in clinical trials. The difference may be associated with a high proportion of patients with stage M1c (78%). On the other hand, 50% of patients after failure of a prior treatment benefited from pembrolizumab, in about 1/3 of patients this clinical benefit was long-lasting.

In the multi-cohort Phase I study KEYNOTE-001 in patients with advanced melanoma 33% of the treated achieved ORR (overall response rate). In this study a total of 655 melanoma patients were treated [135 cohort nonrandomised (n = 87 without ipilimumab pretreatment; n = 48 treated previously with ipilimumab), and 520 were in the randomised cohort (n = 226 without pretreatment ipilimumab; n = 294 after ipilimumab treatment)] [4–7]. Patients received pembrolizumab in different regimens: 10 mg/kg every two weeks, 10 mg/kg every three weeks, or 2 mg/kg every three weeks. Treatment continued until disease progression, unacceptable toxicity, or the investigator's decision to discontinue. The primary endpoint of the study was objective response to the treatment. Analysis ORR concerned 581 patients with measurable disease — a response was acquired in 194 cases [33% (95% CI 30–37%)]. In patients who had not previously received ipilimumab ORR was higher and reached 45% (95% CI 36–54%). Median survival in the overall population was 23 months (95% CI 20–29); survival rate at one-year was 66%, and at two-years it was 49%. Subgroup analysis showed superior OS in patients not previously treated with ipilimumab, amounting to 31 months, with the rate of one-year survival of 73% and 60% at two years. Ninety-two patients (14%) experienced at least one adverse event of grade 3 or 4 treatment-related, and 27 patients discontinued treatment (4%) due to the toxicity. There were no treatment-related deaths. All patients in our group had received prior treatment with ipilimumab.

In a randomised phase II study KEYNOTE-002 the efficacy and safety of pembrolizumab after progression of the disease after ipilimumab therapy was evaluated. Pembrolizumab was compared to chemotherapy (scheme selected by the investigator) [8]. Patients with *BRAF* mutation had previously used *BRAF*, MEK inhibitors alone or in combination. A total of 540 patients were assigned in a 1:1:1 ratio to cohorts receiving pembrolizumab 2 mg/kg every three weeks, 10 mg/kg every three weeks, or chemotherapy (paclitaxel and carboplatin, paclitaxel, carboplatin, dacarbazine, and temozolomide). Blinding of the study concerned only cohorts with pembrolizumab. In patients in these cohorts improvement of PFS was achieved, when compared with those receiving chemotherapy. In the group receiving 2 mg/kg six-month PFS was 34%, and in the 10 mg/kg group it reached 38%, compared with 16% in the chemotherapy group. Treatment responses according to RECIST 1.1 in the pembrolizumab group at a dose of 2 mg/kg were: CR 4 (2%), 34 PR (19%), SD 32 (18%), PD 84 (47%), in the pembrolizumab group with the dose 10 mg/kg CR 5 (3%) and 41 PR (23%) SD 31 (17%) PD 86 (48%). In the chemotherapy group the ORR was CR 0 PR 8 (4%) SD 33 (18%), PD 111 (62%). No significant differences were observed in terms of efficacy between the 2 mg/kg and 10 mg/kg doses. The grade 3 and 4 side effects associated with treatment occurred in 11% of patients in the group of patients receiving pembrolizumab at a dose of 2 mg/kg, in 14% of patients receiving pembrolizumab at a dose of 10 mg/kg, and in 26% in the group receiving chemotherapy. The most common side effects in grade 3 and 4 in patients receiving pembrolizumab were fatigue, generalised oedema, muscle pain, hypopituitarism, colitis, diarrhoea, loss of appetite, hyponatraemia, and pneumonia. In the chemotherapy group the most common toxicities were anaemia, fatigue, neutropaenia, and leukopaenia.

In the phase III study KEYNOTE-006 834 patients participated, with diagnosis of advanced melanoma [9]. The patients were randomly assigned in a 1:1:1 ratio to cohorts receiving pembrolizumab 10 mg/kg every two weeks, pembrolizumab 10 mg/kg given every three weeks, or ipilimumab (3 mg/kg 4 doses every three weeks). The primary endpoints were PFS and OS. The estimated six-month PFS was 47.3% for the groups with pembrolizumab used every two weeks, 46.4% for the group with pembrolizumab given every three weeks, and 26.5% for ipilimumab (HR 0.58, $p < 0.001$ for both schemas of pembrolizumab compared with ipilimumab). Estimated 12-month OS was 74.1%, 68.4%, and 58.2% for two types of dosing of pembrolizumab and ipilimumab, respectively (HR for pembrolizumab administered every two weeks, 0.63; 95% CI 0.47–0.83; p = 0, 0005; HR for pembrolizumab administered every three weeks, 0.69; 95% CI 0.52–0.90; p = 0.0036). Objective response rates were higher for pembrolizumab - in the group receiving the drug every two weeks ORR was 33.7%, in the group receiving pembrolizumab every three weeks ORR was 32.9% *versus* for 11.9% ipilimumab. Median PFS amounted to 5.5 months, 4.1 months, and 2.8 months, respectively. Planned duration of treatment with pembrolizumab was 24 months. Clinical benefit of pembrolizumab in comparison with ipilimumab was independent of the status of the PD-L1 expression, and the *BRAF* mutation. Adverse reactions associated with treatment in grade 3–5 were more frequent in the group receiving ipilimumab (19.9%, including one death) than in the pembrolizumab groups (13.3% and 10.1%). In our material we did not assess the expression of PD-L1 on melanoma cells, but the collective analyses of large groups of patients showed that the expression of PD-L1 in the tumour cells before treatment was correlated with the response rate, PFS, and OS. However, patients without the expression of PD-L1 can also achieve long-term response to treatment [10].

Table 2 shows the incidence of adverse events associated with the immune system in clinical trials, according to the summary of product characteristics [11]. The information relates to patients in clinical trials for advanced melanoma, advanced non-small cell lung

Table 2. Adverse events associated with the immune system during pembrolizumab treatment (n = 2799, ChPL) (%)

Adverse event	Grade 2	Grade 3	Grade 4	Grade 5	Total
Pneumonia	1.3	0.9	0.3	0.1	3.4
Colitis	0.4	1.1	< 0.1	0	1.7
Hepatitis	0.1	0.4	< 0.1	0	0.7
Hypopituitarism	0.2	0.3	< 0.1	0	0.6
Hyperthyroidism	0.8	0.1	0	0	3.4
Hypothyroidism	6.2	0.1	0	0	8.5
Type 1 diabetes	< 0.1	< 0.1	< 0.1	0	0.2
Nephritis	0.1	0.1	< 0.1	0	0.3

cancer, and advanced head and neck cancer; pembrolizumab was used in different schemes — 2 mg/kg every three weeks, 10 mg/kg every two or three weeks, and 200 mg every three weeks. The analysis covers 2799 patients. Most adverse events resolved after adequate treatment. For a small proportion, however, side effects led to cessation of the treatment with pembrolizumab for pneumonia, for instance — it concerned 36 patients, and for colitis — 15 patients. Number of other side that led to cessation of immunotherapy effects are as follows: hepatitis — six patients; hypopituitarism — four patients; hyperthyroidism — two patients; hypothyroidism — one patient; and nephritis — three patients. In total 67 patients (2%) ended treatment due to adverse events.

In our centre we treated two patients with ocular melanoma — no responses to treatment were obtained. Similarly, in the KEYNOTE-001 study, in 20 patients with this diagnosis there was no response to therapy. However, there are reports of activity of pembrolizumab in patients with diagnosis of ocular melanoma — at the ASCO conference in 2015 data on eight patients were presented — one had a complete remission of the disease and two had partial remission [12].

Conclusions

Pembrolizumab confirmed its activity and safety profile for use outside of clinical trials in patients previously overtreated due to metastatic melanoma. Treatment with anti-PD-1 antibodies is the preferred therapeutic option for patients with advanced melanoma [13, 14].

Acknowledgements

We would like to thank MSD for providing the drugs for our patients.

Potential conflict of interest

P. Rutkowski received lecture fees from Roche, MSD, BMS, Novartis, Pfizer, and participated in the Advisory Board for Novartis, Roche, Amgen, BMS, and MSD.

References

1. Rutkowski P. (ed). Nowe terapie w czerniakach. Via Medica Gdańsk 2016.
2. Mahoney KM, Freeman GJ, McDermott DF. The Next Immune-Checkpoint Inhibitors: PD-1/PD-L1 Blockade in Melanoma. Clinical Therapeutics 2015; 37.
3. Rutkowski P, Ługowska I, Świtaj T. Pembrolizumab. Biblioteka czasopisma Onkologia w Praktyce Klinicznej. Via Medica, Gdańsk 2015.
4. Robert C, Ribas A, Wolchok JD et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384: 1109–1117.
5. Hamid O, Robert C, Daud A et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med 2013; 369: 134–144.
6. Patnaik A, Kang SP, Rasco D et al. Phase I study of pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in patients with advanced solid tumors. Clin Cancer Res 2015; 21: 4286–4293.
7. Daud A, Ribas A, Robert C et al. Long-term efficacy of pembrolizumab (pembro;MK-3475) in a pooled analysis of 655 patients (pts) with advanced melanoma (MEL) enrolled in KEYNOTE-001. ASCO 2015, abstract nr 9005.
8. Ribas A, Puzanov I, Dummer R et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015; 16: 908–918.
9. Robert C, Schachter J, Long GV et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015; 372: 2521–2532.
10. Daud AI, Wolchok JD, Robert C et al. Programmed Death-Ligand 1 Expression and Response to the Anti-Programmed Death 1 Antibody Pembrolizumab in Melanoma. J Clin Oncol 2016; 34: 4102–4109.
11. Charakterystyka Produktu Leczniczego Keytruda, EMA 2016.
12. Kottschade LA, McWilliams RR, Markovic S et al. The use of pembrolizumab for the treatment of metastatic uveal melanoma. J Clin Oncol 2015; 33 (suppl.), abstract 9009.
13. Homet Moreno B, Ribas A. Anti-programmed cell death protein-1/ligand-1 therapy in different cancers. Br J Cancer 2015; 112: 1421–1427.
14. Dummer R. Cutaneous Melanoma: ESMO Clinical Practice Guidelines. Ann Oncol 2015; 26 (suppl. 5): v126–v132.
15. Melanoma v. 3.2016. NCCN.org.