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REVIEW ARTICLE

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Summary of immunotherapy efficacy ordered in accordance with drug reimbursement program in melanoma patients

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ABSTRACT

Nivolumab and pembrolizumab are monoclonal antibodies of the IgG4 class, which target the cell death receptor (PD-1) found on T cells. The binding of the anti-PD-1 drug to the receptor therefore prevents the inhibition of these T cells and increases the immune response against melanoma cells. Pembrolizumab and nivolumab monotherapy has similar efficacy, including PFS and OS. Nivolumab and pembrolizumab immunotherapy are effective regardless of the *BRAF* mutation status. Currently, the choice between nivolumab and pembrolizumab is primarily dependent on to the frequency of infusions (every 3 weeks for pembrolizumab *vs.* every 2 weeks for nivolumab or every 6 weeks *vs.* every 4 weeks). Based on the available data, it can be concluded that autoimmune disease is not an absolute contraindication to the use of immunotherapy, but close clinical monitoring of these patients and specialist consultations (e.g. rheumatologist, dermatologist) must be provided. Patients with severe autoimmune disease who are treated with biologicals or have a history of life-threatening autoimmune disease complications (e.g. severe Crohn's disease) should not be qualified for immunotherapy, as opposed to patients with minimally symptomatic autoimmune disease (e.g., mild dermal psoriasis).

Key words: melanoma, immunotherapy, nivolumab, pembrolizumab

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Introduction

The relatively recent registration of immunotherapy initiated a significant change in treating patients diagnosed with advanced melanoma. Before 2011 patients with melanoma in the dissemination stage were treated palliatively by chemotherapy (dacarbazine), and this treatment did not prolong overall survival. In 2019, because of the registration and refunding of immunotherapy, patients with melanoma could obtain long-term responses and overall survival (OS), including complete responses (CR) to treatment. The basis of immunotherapy in patients with advanced melanoma is antibodies directed against the programmed death cell receptor-1 (PD-1) — pembrolizumab and nivolumab, used in monotherapy or in combination therapy with antibodies directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) — ipilimumab. Ipilimumab is an antibody registered in 2011 directed against the CTLA-4 protein, which was the first to give a significant prolongation of overall survival with a simultaneous low percentage of responses (approx. 10%). In prospective clinical trials the advantage of PD-1 inhibitors such as pembrolizumab and nivolumab over anti-CTLA4 antibodies was demonstrated in first-line melanoma treatment in the form of a greater chance of obtaining objective responses (overall response rate; ORR) to treatment and longer progression-free survival (PFS), as well as longer overall survival. Nivolumab and pembrolizumab are monoclonal antibodies of the IgG4 class, which attach to the cell death receptor PD-1 on

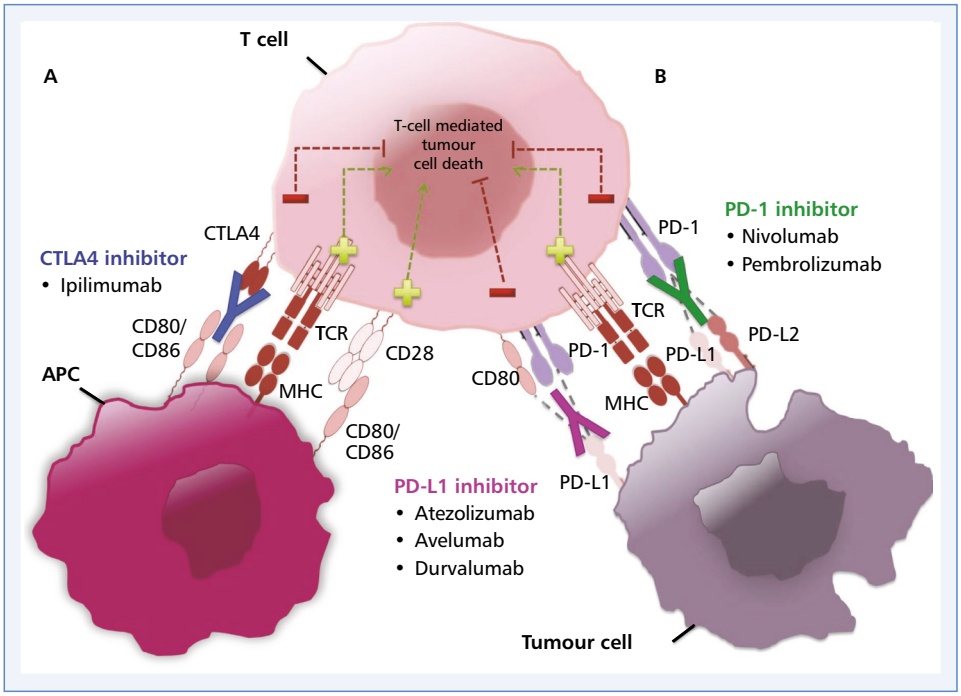

Figure 1. Mechanism of immunotherapy action [1]. In the first stage of the immune response, naive T cells in lymphatic organs (e.g. lymph nodes) are presented with antigens specific for the neoplasm, which causes the differentiation of naive T cells into effector T cells (e.g. Treg, cytotoxic T cells, and helper T cells). This process is intensified by a co-stimulating signal from the CD28 receptor from CD80/86. CD28 activation is inhibited in the presence of the CTLA-4 receptor, which has a much higher affinity for CD80/86 ligands. Antibodies blocking CTLA-4 prevent this inhibition and stimulate the maturation of effector T cells capable of an anti-neoplasm response. Moreover, anti-CTLA-4 antibodies can be involved in inhibition of Treg cells in the tumour microenvironment. In the effector phase of the immune response cytotoxic cells in the tumour microenvironment eliminate tumour cells; however, their activity is suppressed by interactions between the PD-1 receptor on T cells and PD-L1 or to a smaller extent PD-L2 on the surface of tumour cells and macrophages in the tumour. Inhibition of the PD-1/PD-L1 pathway enables T cell activation and restores T cell response against neoplasm cells

CD4+, CD8+ T lymphocytes, B lymphocytes, and myeloid cells and prevent the death of immune system cells. The binding of the anti-PD-1 drug to the receptor prevents the inhibition of the functions of these cells and strengthens the immune response to neoplastic cells (Figure 1) [2].

Treating patients without the *BRAF* mutation

Currently, melanoma patients without a mutation in the *BRAF* gene (*BRAF-WT*) in the frame of the drug program for treatment of cutaneous and mucosal melanoma (ICD-10 C43) can be treated in the first line by nivolumab or pembrolizumab in monotherapy, and the choice of the drug is left to the decision of the attending physician after a discussion with the patient (Figure 2). Both drugs were registered on the basis of phase III trials [4, 5].

The registration trial evaluating the effectiveness of first-line treatment with nivolumab in monotherapy in patients with a diagnosis of locally advanced non-resectable or metastatic melanoma *BRAF-WT* was the CheckMate066 trial (NCT01721772). The trial included 418 patients who were randomly assigned in a ratio of 1:1 to treatment with nivolumab administered at a dose of 3 mg/kg body mass every two weeks or the branch with dacarbazine administered at a dose of 1000 mg/m^2 body surface, and the treatment was continued until disease progression or unacceptable toxicity. In the nivolumab group the median age of the patients was 64 years (range 18–86 years) and 57.6% were men; for dacarbazine the median age was 66 years (range 25–87 years) and 60.1% were men. The median progression-free survival (PFS) was 5.1 months for nivolumab treatment and 2.2 months for dacarbazine treatment (HR = 0.43; 95% CI: 0.34–0.56; P < 0.001). The ORR percentage was 40% for persons treated with nivolumab and 13.9% for those treated with dacarbazine [6]. After more than 38 months

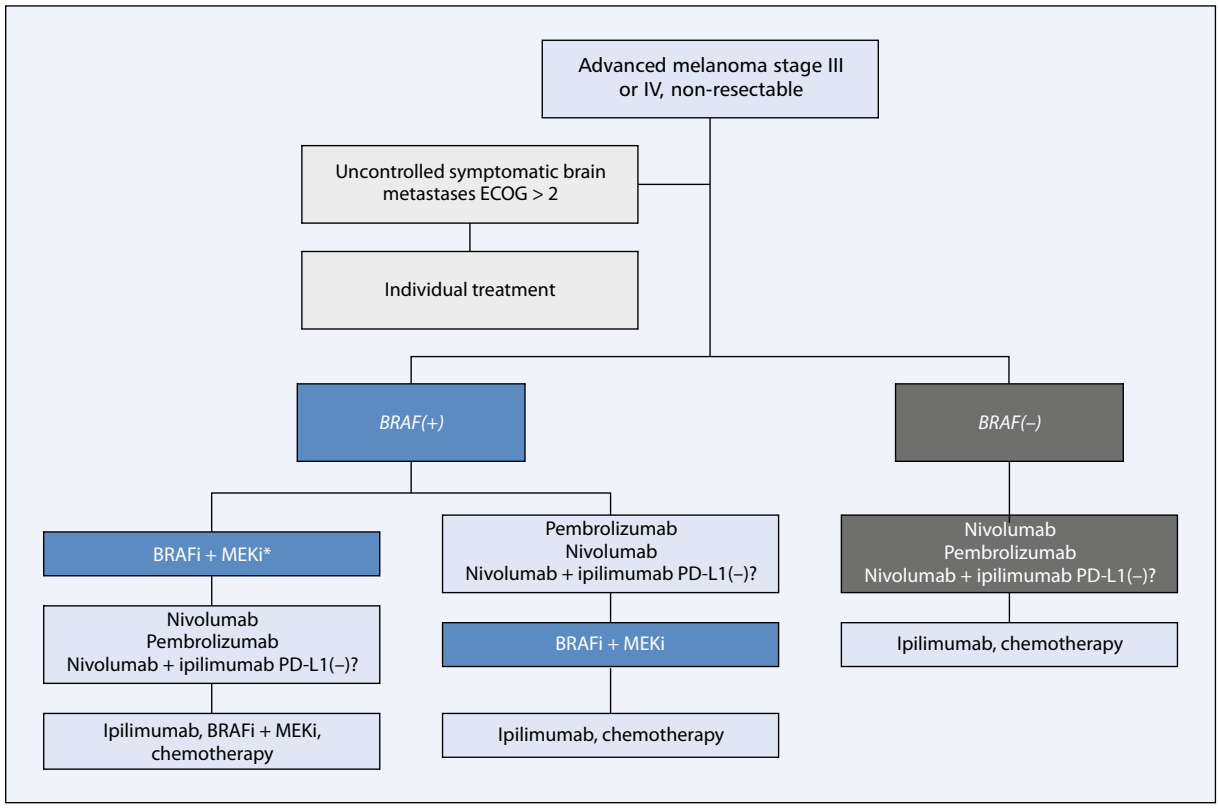

Figure 2. Scheme of systemic melanoma treatment including immunotherapy [3]. **?** — indication registered but not reimbursed; *— dabrafenib + trametinib, vemurafenib + cobimetinib or encorafenib + binimetinib

of observation in the group treated with nivolumab three-year OS indices were 51.2% (95% CI, 44.1–57.9) and in the group treated with dacarbazine — 21.6% (95% CI, 16.1–27.6). The median OS was 37.5 months (95% CI, 25.5 months–not reached) in the nivolumab group and 11.2 months (95% CI, 9.6–13.0 months) in the group treated with dacarbazine (risk coefficient 0.46; 95% CI, 0.36–0.59; $P < 0.001$) (Figure 3). At the moment of data analysis 63.8% (134 of 210) of patients in the nivolumab group had disease progression or died, in comparison to 82.7% (172 of 208) of patients in the dacarbazine group, and three-year PFS indices were 32.2% (95% CI, 25.6–39.0) and 2.9% (95% CI, 0.7–8.1), respectively. Subgroup analysis indicated that in patients with PD-L1 expression of at least 5% the median OS was not reached (95% CI, 4.4–NR) in the nivolumab treatment group and was 9.7 months (95% CI, 6.7––13.5 months) in the dacarbazine treatment group. In patients with PD-L1 expression lower than 5% the median OS during nivolumab treatment was 28.2 months (95% CI, 18.2–38.5 months) and 11.6 months (95% CI, 9.3–13.0 months) for patients treated with dacarbazine. Similarly, regardless of PD-L1 expression, patients in the group treated with nivolumab had longer progression-free survival in comparison to patients from the group treated with dacarbazine — CR and partial response (PR) were noted in 19.0% (40 of 210) and 23.8% (50 of 210) of patients, respectively, in the group treated with nivolumab in comparison to 1.4% (3 of 208) and 13.0% (27 of 208) of patients in the group treated with dacarbazine. Treatment-related undesirable effects of the third/fourth degree occurred in 15.0% (31 of 206) of patients treated with nivolumab and in 17.6% (36 of 205) of patients treated with dacarbazine, and no deaths due to the toxicity of either of the drugs were observed [7].

The first trial evaluating the treatment effectiveness of pembrolizumab in monotherapy in first-line treatment in patients with nonresectable or metastatic melanoma was the KEYNOTE-001 trial, in which 655 patients were randomised into melanoma cohorts; 151 of them had not been treated previously, and 496 had been treated (205 received one previous therapy, 178 received two previous therapies, 113 received three or more previous therapies). At the moment of data analysis 63% (n = 412) of all patients had died and 54% (n = 81) of all previously untreated patients had died. In a three-year analysis in previously untreated patients the median OS was 31 months (95% CI, 24–NR), with a 12-month survival index of 73% (95% CI, 65–79) and a 24 month survival index of 60% (95%

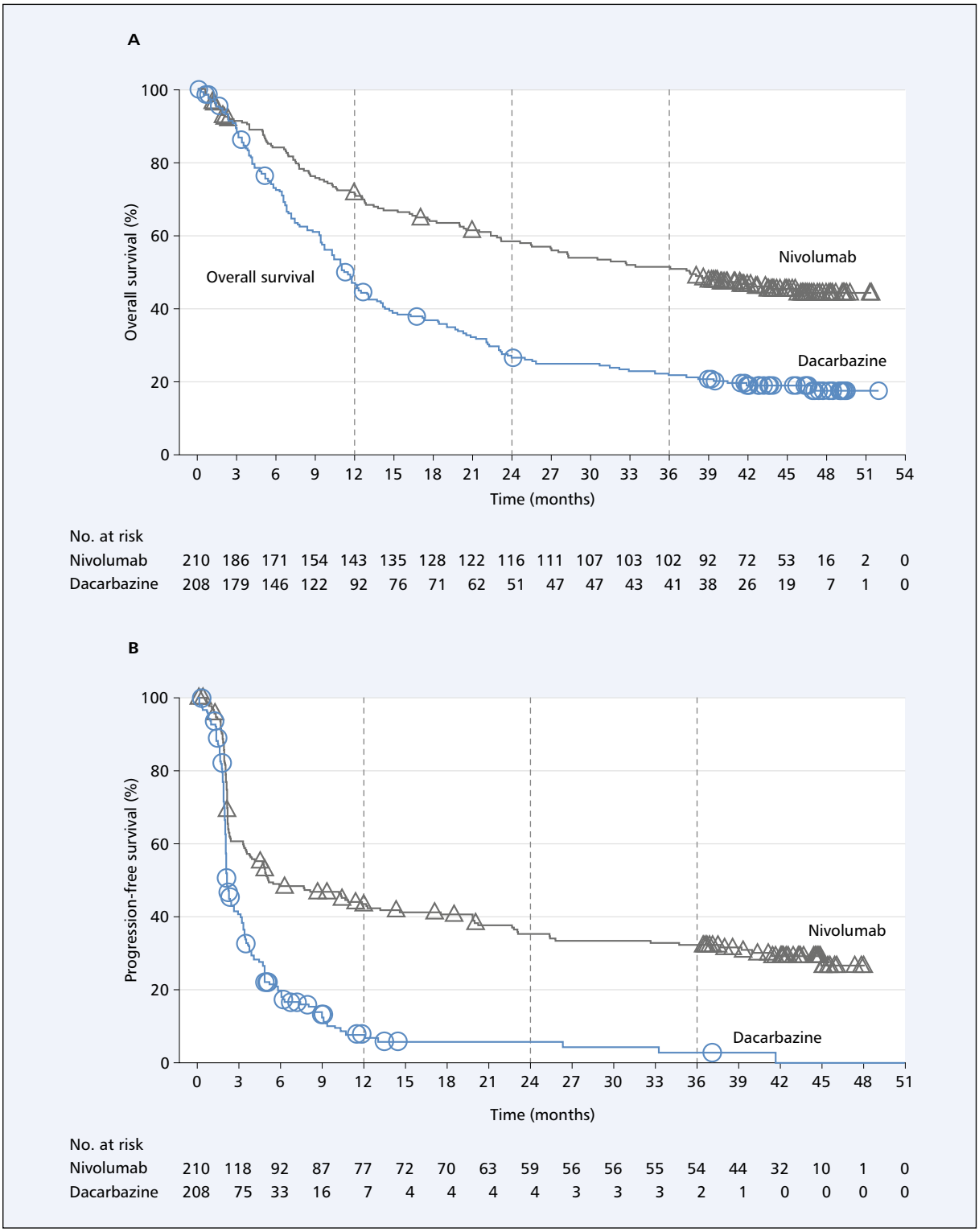

Figure 3. Long-term overall survival (**A**) and time to disease progression (**B**) in melanoma patients without the *BRAF* gene mutations treated with nivolumab in first-line treatment [7]

CI, 51–68) [8]. The estimated index of five-year OS was 34% in the whole patient cohort and 41% in previously untreated patients. Median OS was 23.8 months (95% CI, 20.2–30.4) in the whole cohort and 38.6 months (95% CI, 27.2–NR) in previously untreated patients (Fig. 1A and B). The five-year estimated PFS index was 21%

and 29%, respectively. Median PFS was 8.3 months (95% CI, 5.8–11.1) in the whole cohort and 16.9 months (95% CI, 9.3–35.5) in previously untreated patients. In those treated with pembrolizumab as first-line treatment CR was reached by 38 patients (25%), 40 (27%) reached PR, and 30 (20%) had stable disease (SD), and finally 32 patients (21%) had progressive disease (PD). Median time to response in patients treated in the first line was 2.8 months (range: 2.5–32.0), and the median time of maintained response was not attained (range: 1.3+ to 60.8+ months). Among 38 patients who reached CR, median time to response was 2.8 months (range: 2.5–8.3), and median time of response duration was also not attained (range: 6.0+ to 60.8+ months). The response was still present in 35 patients (92%) at the moment of data analysis. Among 40 patients who attained PR, median time to response was 2.8 months (range: 2.5–32.0), and median time of response duration was also not attained (range: 1.3+ to 51.4+ months), and in the 29 previously untreated patients (73%) who reached PR at the moment of data analysis the response was still ongoing. In this trial in the whole analysed population 156 (24%) patients had a diagnosis of *BRAF*+ melanoma [9].

The second trial in which first-line pembrolizumab treatment was given to patients with melanoma in the dissemination stage was the KEYNOTE-006 trial. Pembrolizumab and ipilimumab treatments were compared. Among patients who received pembrolizumab as first-line treatment the median OS was 38.7 months *vs*. 17.1 months (HR = 0.73, p = 0.0036) for those treated with ipilimumab, and median PFS was 11.6 months *vs*. 3.7 months (HR = 0.54, P < 0.0001). The patients who were not treated in the first line were those who had previously received chemotherapy (14% for pembrolizumab and 10% for ipilimumab), BRAF or MEK inhibitors (17% and 20%), or immunotherapy (3% and 4%). In patients receiving second-line treatment with pembrolizumab the median OS was 23.5 months in comparison with 13.6 months (HR = 0.75, P = 0.036) for ipilimumab treatment [10]. In the previously untreated population, the percentage of ORR was 39.4% (95% CI, 34.4–44.6%) for pembrolizumab treatment in comparison with 13.3% (95% CI. 8.7–19.1%) for ipilimumab. Median time to response was 12.1 weeks (range 3.7––48.1 weeks) and 12.6 weeks (range 11.4–42.4 weeks), respectively, and the median time of response duration was not attained in any of the groups (range: 7.7–99.1+ weeks with pembrolizumab and 4.7+ to 95.9+ weeks with ipilimumab). When pembrolizumab was used the best complete response was CR in 52 patients (14.1%), and PR occurred in 93 (25.3%); 40 (10.9%) had SD. For ipilimumab CR was obtained in seven patients (3.9%), PR in 17 (9.4%), and 30 (16.6%) had SD [11]. In the KEYNOTE-006 trial in patients with *BRAF-WT* melanoma median OS was 28.1 months for pembrolizumab treatment *vs.* 13.9 months for ipilimumab treatment (HR = 0.73, P = 0.0048) (Figure 4). In patients with the *BRAF* gene V600E mutation or a *BRAF* V600K mutation previously treated with BRAF or MEK inhibitors median OS was 20.4 months for pembrolizumab treatment in comparison with 11.9 months for ipilimumab treatment (HR = 0.71, p = 0.054). In patients with melanomas with the *BRAF* V600E or V600K mutation not treated previously with BRAF or MEK inhibitors (patients with initial normal levels of lactate dehydrogenase) median OS was not attained during pembrolizumab treatment in comparison with 26.2 months during ipilimumab treatment (HR = 0.70, P = 0. 065) [10].

Comparison of nivolumab and pembrolizumab use

Monotherapy with pembrolizumab or nivolumab has similar effectiveness, including the range of PFS and OS (Figure 5). Currently the choice between nivolumab and pembrolizumab also concerns, above all, the frequency of infusions (every three weeks for pembrolizumab in comparison with every two weeks in the case of nivolumab or every six, as compared to every four weeks). An American analysis based on the evaluation of the Flatiron Health Inc. Database encompassing data from over 280 regional oncological centres, seven main academic research centres and 15 leading oncological companies described 888 patients with advanced melanoma, of whom in the first line 486 patients were treated with pembrolizumab and 402 patients with nivolumab. In 58% patients treated with nivolumab a constant 240 mg dose was administered every two weeks, and in the 38% of patients treated with pembrolizumab — 200 mg every three weeks, the remaining patients were treated using doses calculated per kilogram body weight. Median OS for patients treated with pembrolizumab was 22.6 months and for those treated with nivolumab — 23.9 months (P = 0.91), and no differences were found in survival between patients treated with pembrolizumab and nivolumab (HR 1.10; 95% CI, 0.87–1.39). Similar results were obtained in clinical practice within the framework of drug programs of melanoma treatment in the Centre for Oncology in Warsaw (Figure 6). Because of the lack of significant differences in the effectiveness of nivolumab in comparison to pembrolizumab an additional factor supporting the decision as to the choice of drug can be the toxicity profile of the anti-PD-1 drug, which is different depending on the drug and should be considered in respect to the accompanying diseases and the patient's age [13].

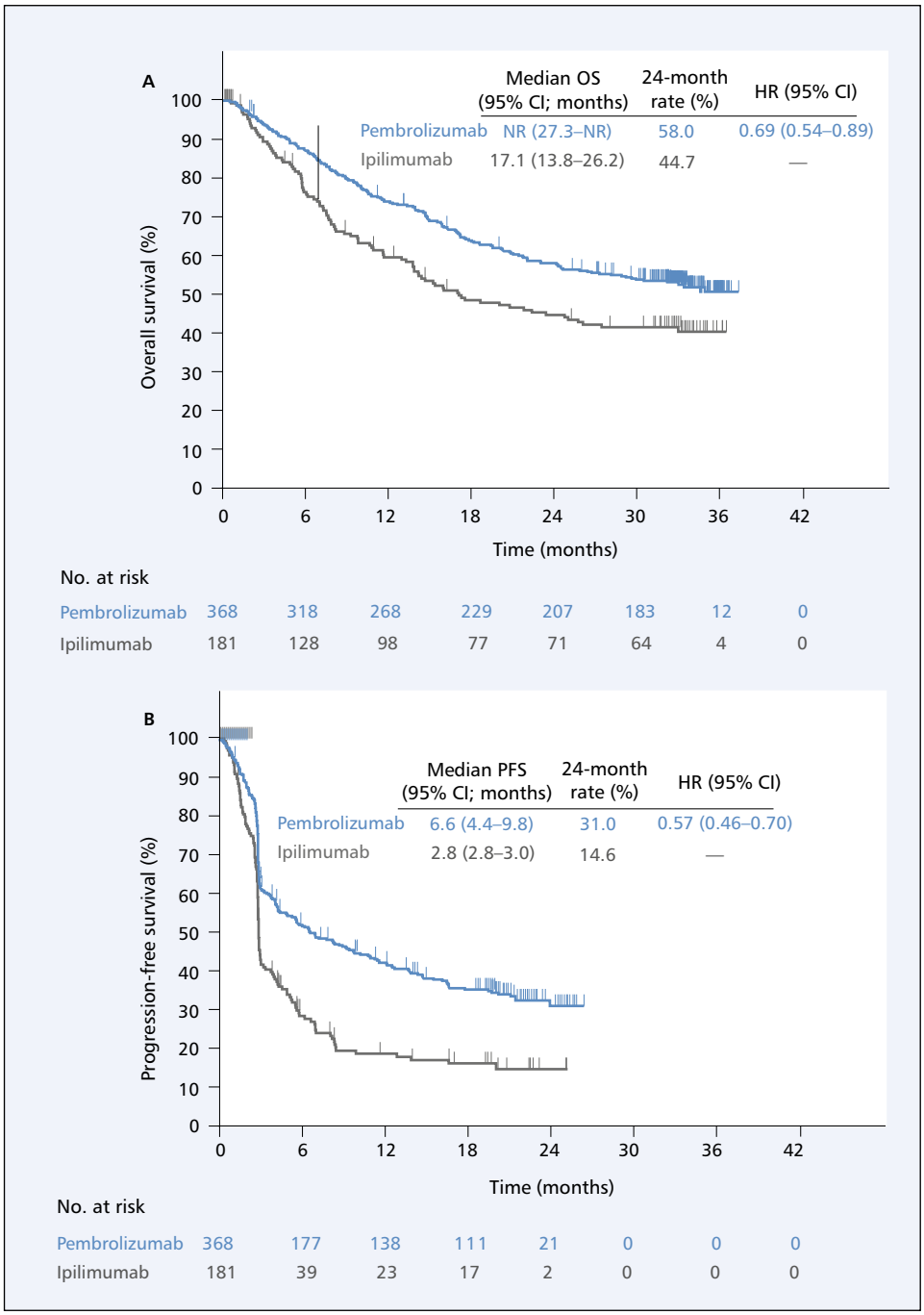

Figure 4. Long-term overall survival (**A**) and time to disease progression (**B**) in melanoma patients treated with pembrolizumab in first-line treatment [11]. NR — not reached

Treatment of patients with the *BRAF* mutation

Immunotherapy with anti-PD-1 antibodies (nivolumab, pembrolizumab) is effective regardless of the *BRAF* mutation status [14]. Analysis of treatment of patients included in the CA209-003 (NCT00730639), CA209--038 (NCT01621490), CA209-004 (NCT01024231), and CA209-037 (CheckMate037, NCT01721746) trials showed that for nivolumab treatment the median time of OR duration is 14.8 months (95% CI, 11.1–24.0 months) for melanoma patients without the *BRAF* gene mutation (*BRAF-WT*) and 11.2 months (95% CI, 7.3–22.9 months) for melanoma patients with *BRAF* gene mutations (*BRAF+*). ORR was 34.6% for patients with B*RAF-WT* (75 responses for 217 cases)

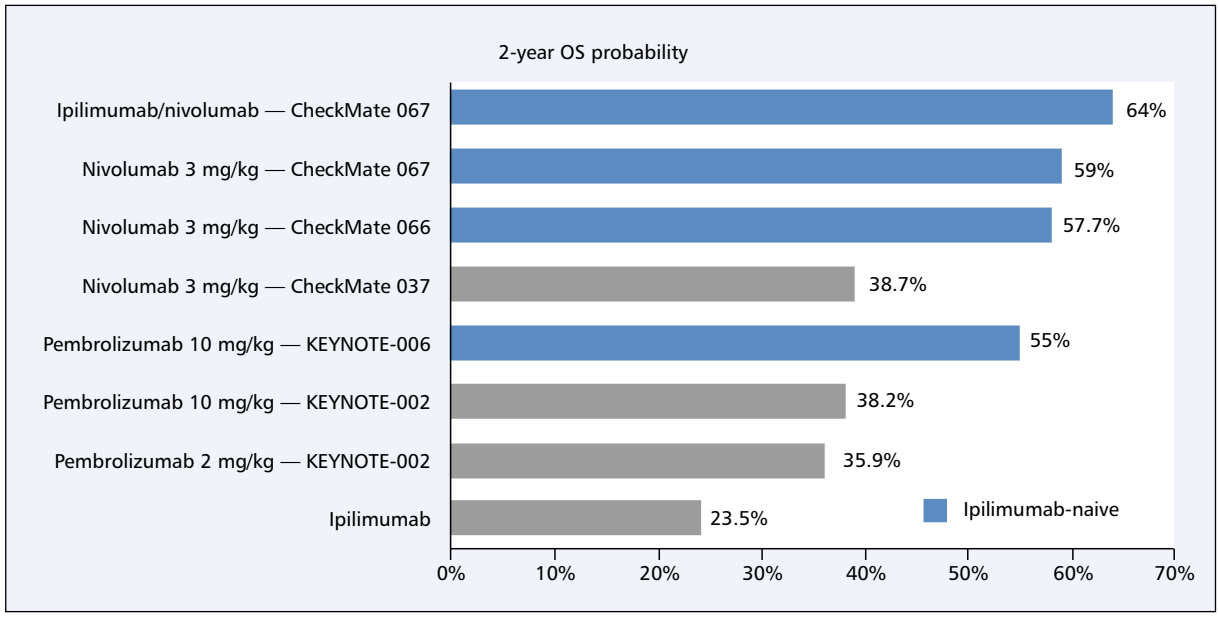

Figure 5. Overall survival index after two years of anti-PD-1 therapy in advanced sarcoma [12]

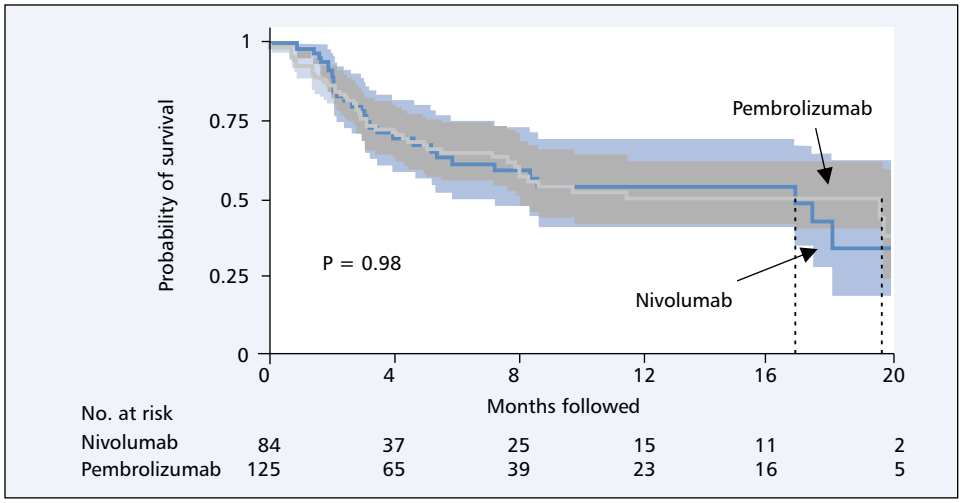

Figure 6. Overall survival time during nivolumab and pembrolizumab treatment (own data)

and 29.7% for patients with *BRAF+* (22 responses for 74 cases). Median time of OR duration was similar in patients with B*RAF-WT* (14.8 months; 95% CI, 11.1–24.0) and *BRAF+* (11.1 months; 95% CI, 7.3–22.9) [14]. In a more recent trial, CheckMate 067, also evaluating combined immunotherapy, it was shown that in the first line of treatment of patients with *BRAF+* melanoma after 28 months of observation median OS was not attained in the group treated with nivolumab with ipilimumab nor in the group treated with nivolumab and was 24.6 months in the ipilimumab group (95% CI, 17.9–33.0). In this group of patients with *BRAF+* melanoma the two-year overall survival OS was 71% for the combination, 62% for nivolumab, and 51% for ipilimumab [15]. The general indirect comparison of the effectiveness of BRAFi/MEKi and checkpoint inhibitors in patients with *BRAF+* melanoma indicates the superiority of molecularly directed therapies during the first 5–6 months, and the superiority of anti-PD-1 treatment or together with CTLA-4 in successive months of treatment. The first meta-analysis published in 2017 suggests that BRAFi/MEKi treatment is the most effective in the scope of improving OS, PFS, and ORR in patients with *BRAF+* melanoma, and is superior to immunotherapy in this area [16]. In turn, a Cochrane analysis indicated the superiority of immunotherapy in the scope of treat-

ment safety, and the superiority of BRAFi/MEKi in the scope of prolonging PFS [17]. The most recent analysis only comparing immunotherapy with a combination of nivolumab and ipilimumab *vs*. BRAFi/MEKi therapy indicated a statistically significant advantage in the scope of OS for nivolumab and ipilimumab in comparison with both schemes of BRAF and MEK inhibitors. For therapy a comparison of nivolumab + ipilimumab versus dabrafenib + trametinib HR (95% CI) was calculated as 0.64 (0.46, 0.89) and for nivolumab + ipilimumab *versus* vemurafenib + cobimetinib treatment — 0.56 (0.36, 0.89) [18]. However, so far, no randomised clinical trial comparing BRAFi/MEKi (dabrafenib + trametinib, vemurafenib + cobimetinib or enkorafenib+binimetinib) and immunotherapy (nivolumab or pembrolizumab) has been published, which does not allow the evaluation of optimal first-line treatment for patients with *BRAF*+ melanoma.

The optimal sequence of treatment with BRAF and MEK kinase inhibitors (BRAFi/MEKi) and immunotherapy is not defined at present. So far, there are no available prospective data from randomised trials allowing us to determine the best sequence of treating patients with *BRAF*+ melanoma. In particular, there are no prospective data concerning sequential treatment in patients with poor prognostic factors. The currently published joint analysis of phase II and III trials indicated that in the case of nivolumab treatment neither earlier therapy with BRAFi nor earlier treatment with ipilimumab have an effect on ORR. In this analysis ORR was 33.1% in *BRAF*+ patients without prior BRAFi treatment and 24.5% in patients who had previously received BRAFi. However, the direct interpretation of results is difficult because in patients treated with nivolumab earlier therapy with a BRAF inhibitor was applied in 71.7% (76) of *BRAF*+ patients, but in 85.8% (91) also more than two schemes of earlier treatment had been applied, including chemotherapy and ipilimumab according to inclusion criteria for the CheckMate 003, CheckMate 004, CheckMate 037, and CheckMate 038 trials [14].

The oldest analyses, because of the time of drug registration, evaluated the application of BRAFi/MEKi after ipilimumab. In the analysis by Ackerman et al. 274 patients with advanced melanoma with a *BRAF* mutation were evaluated, and the percentages of ORR, PFS, and OS were compared among patients who received immunotherapy (including high doses of interleukin 2, nivolumab, ipilimumab, or adoptive cell therapy) before directed therapy (encompassing vemurafenib in monotherapy, dabrafenib in monotherapy, and dabrafenib together with trametinib). In BRAFi treatment — 117 received vemurafenib, 99 — dabrafenib, and 58 — dabrafenib and trametinib. In this analysis RR, median PFS and OS for second-line BRAFi treatment (after immunotherapy with ipilimumab) was 57%, 6.7 months (n = 32, 95% CI, 4.3–9.1 months), and 19.6 months (95% CI, 10.0–NR months), respectively. At the same time, for first-line use of BRAFi (n = 242) these data were 66% RR, 5.6 months PFS (95% CI, 4.7–6.8 months), and 13.4 months OS (95% CI, 10.1–177.0 months). In these patients the response to targeted therapy was similar whether it was given before or after immunotherapy, but ORR and survival for the group treated with ipilimumab were better if it was used before targeted therapy. On the basis of such results the authors of the analysis concluded that the use of immunotherapy with ipilimumab as first-line treatment does not appear to negatively affect the response to BRAFi therapy [19]. Similarly, in the analysis by Ascierto et al. patients who received ipilimumab before targeted therapy had better OS in comparison with patients treated by targeted therapy and then ipilimumab [20]. On the basis of these two trials it began to be suggested that in the case of sequential treatment immunotherapy should be used first. Newer analyses also confirmed that ORR indices are lower in the case of ipilimumab therapy after progression to BRAFi; therefore, it was suggested that administering immunotherapy in the first line may be the best mode of action [21].

Current analyses are evaluating the use of BRAFi/MEKi after anti-PD1 therapy. In the analysis of Johnson et al. patients who received in the first line anti-PD-1 therapy (n = 56) were compared with those who were first treated with BRAFi/MEKi (n = 58). These two groups of patients had different PFS in second-line treatment, but median OS did not differ significantly between the groups (27.5 *vs*. 40.3 months, P = 0.71). Patients with progression on anti-PD-1 treatment had shorter survival after initiation of second-line BRAFi/MEKi therapy with as median PFS of five months and median OS of 10.6 months. The ORR index of anti-PD-1 therapy seemed to be slightly higher in the group not previously treated with BRAFi (first anti-PD-1) (41% *vs.* 25%) [19]. The most recent analyses have indicated that BRAFi/MEKi given after anti-PD-1 therapy is less effective, and it was suggested that there could be a common mechanism of resistance to the two treatment methods [22].

Summing up, it is now known that both BRAFi/MEKi therapy as well as immunotherapy (anti-PD-1 monotherapy) are effective methods of treating patients with *BRAF*+ melanoma in the dissemination stage, and long-term responses are observed in both subgroups of patients, regardless of earlier therapies. In patients with a good performance status and proper organ function, anti-PD-1 treatment can be considered regardless of the status of the *BRAF* mutation. However, clinicians should maintain particular care in qualifying patients with an initially unfavourable prognosis for treatment. The

results of the analysis of registration trials (nivolumab, pembrolizumab) cannot be directly transferred to patients who do not fulfil the qualification criteria for these trials, for instance patients with a poor performance status, because the percentages of responses to immunotherapy may not be similar in patients with *BRAF*-WT and *BRAF*+ melanomas in patients with high LDH, metastases to the CNS, or a large tumour mass and metastases to many parenchymal organs. Moreover, the optimal sequence of BRAFi/MEKi therapy and immunotherapy in treating patients with melanoma is still under discussion and is the subject of evaluation of four ongoing clinical trials (SECOMBIT, EBIN, i.e. EORTC 1612-MG and ECOG-ACRIN SWITCH, i.e. EA6134 and DREAMseq). It should, however, be pointed out that all these ongoing trials encompass in one arm combined immunotherapy (anti-PD-1 and anti-CTLA-4), whereas SECOMBIT and EBIN analyse the combination of encorafenib with binimetinib, and these strategies are currently not available in Poland in the scope of drug programs. It seems that the ongoing trials will determine the effect of the sequence of therapy directed against BRAF and the blocking of PD-1 and/or CTLA-4 on the results of treatment and survival of patients with melanoma in the dissemination stage. Clinical trials encompassing blocking PD-1, and also new trials of combinations of various immunotherapies or the analysis of combinations of targeted therapies may be considered as the first line of therapy options for all patients with advanced melanoma [23].

Immunotherapy and immunosuppression and autoimmune diseases

At present the meta-analysis of data or diagnostic-therapeutic recommendations concerning the safety and effectiveness of anti-PD-1 and anti-CTLA-4 antibodies in patients with previously existing autoimmune diseases are not available. A population epidemiological analysis performed in the USA indicated that this is a significant clinical problem concerning as many as one in five patients. The occurrence of prior autoimmune diseases in melanoma patients was calculated. Among 12,028 patients with newly diagnosed melanoma in the dissemination stage the frequency of occurrence of autoimmune diseases rose from 17.1% in 2004 to 28.3% in 2014 [24]. A similar frequency of autoimmune diseases can be expected in the Polish population among patients who are to start treatment in the Drug Program of treating melanoma by immunotherapy [25, 26]. Data available so far indicate the possibility of using systemic treatment of melanoma by immunotherapy in selected patients from this group.

In a multicentre trial directed by Melanoma Institute Australia and the University of Sydney in patients treated using anti-PD1 immunotherapy for melanoma in the dissemination stage with an existing autoimmune disease (N = 52) the percentage of responses was 33%. During anti-PD-1 immunotherapy exacerbations occurred in patients with rheumatological problems (14/27), psoriasis (3/8), Graves' disease (1/4), and immunological thrombocytopaenic purpura (2/2). Moreover, 20 (38%) patients had autoimmune disease exacerbations that required immunosuppression; these were patients with rheumatoid arthritis (7/13), rheumatic polymyalgia (3/3), Sjogren's syndrome (2/2), immunological thrombocytopenic purpura (2/2), and patients with psoriasis (3/8). Only two (4%) patients stopped treatment because of exacerbation of their autoimmune disease, and no deaths linked to treatment were noted. Clinical recurrence or an increase of previous symptoms were described (e.g. joint pain in patients with rheumatoid arthritis, increased skin symptoms in psoriasis patients), but not the occurrence of new disease symptoms (e.g. new lung symptoms in patients with rheumatoid arthritis). Exacerbations were more common in persons with active symptoms at the moment of ipilimumab treatment initiation (9/15, 60%) than in patients with clinically inactive disease (11/37, 30%) (P = 0.039). A tendency was also described of an increase in the number of exacerbations in persons receiving immunosuppressive drugs at the time of initiation of systemic melanoma treatment (10/20, 50%) in comparison with patients not requiring the administration of immunosuppressive drugs (10/32, 31%) (P > 0.05) at the time of qualification for immunotherapy. It is worth noting, however, that two of seven patients taking steroid drugs at the beginning of the treatment obtained an objective response, but none of the patients receiving other immunosuppressive drugs (including methotrexate); also, no objective responses were noted in patients who were taking steroids in combination with another immunosuppressive drug, which appears to be linked to the immunosuppressive mechanism of steroids and methotrexate (Figure 7), which prevent lymphocyte activation induced by immunotherapy (Figure 1) [30]. Analogous data have been published for ipilimumab treatment. Thirty patients were evaluated; they received ipilimumab and concurrently: six had rheumatoid arthritis, five — psoriasis, six — inflammatory bowel disease, two — systemic lupus erythematosus, two — multiple sclerosis, two — autoimmunological thyroid inflammation, and seven had other diseases. In the analysed cohort 13 patients (43%) were receiving immunosuppressive treatment at the moment of initiating ipilimumab treatment, most commonly with small doses of prednisone or hydroxychloroquine. During ipilimumab treatment eight patients (27%) had exacerbation of their immunological disease requiring

systemic treatment, but all were sufficiently controlled by corticosteroids. Undesirable effects dependent on the immunological mechanisms in degree 3 to 5 occurred in patients (33%) and were reversible after using corticosteroids or therapy with infliximab in two cases, but one patient with a psoriasis diagnosis died because of colon inflammation. At the same time in 15 patients (50%) neither exacerbation of the autoimmune disease nor irAE were observed. In six patients (20%) objective responses were described, including one with a persistent CR [31]. Finally, the most recent research has shown that it is still unclear whether the number of life-threatening and fatal complications is small in patients with autoimmune diseases treated with immunotherapy because one meta-analysis (of patients with all types of neoplasms) indicated that fatal toxic action was observed in three out of 123 patients [32].

Currently, trial NCT03140137 is ongoing (112 patients are to be analysed) to determine the tolerance of immunological checkpoint inhibitors in patients with prior autoimmune diseases. Trial NCT03816345 (AIM-NIVO) will evaluate the safety of using nivolumab in patients

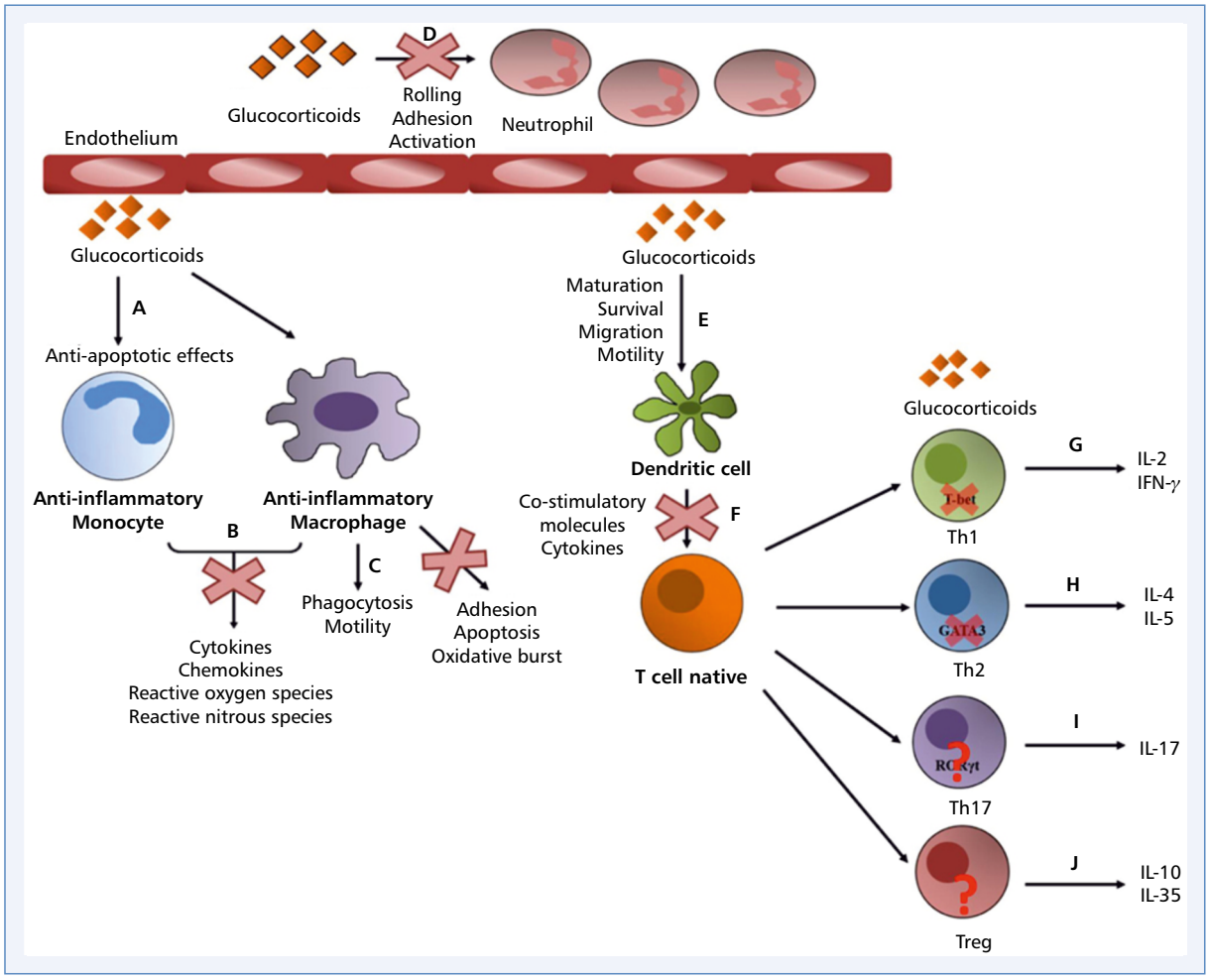

Figure 7A. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — effect of steroid drugs on cells of the immune system [27]. Glucocorticoids act on almost all types of cells of the immune system and promote an anti-inflammatory state in both monocytes and macrophages. They prevent monocyte apoptosis (**A**) and inhibit the liberation of proinflammatory mediators by monocytes and macrophages (**B**). In macrophages they promote phagocytosis and mobility, inhibiting adhesion, apoptosis, and oxygen burst (**C**). They also act on neutrophil function by inhibiting their movement, adhesion to the substrate, and activation (**D**). Steroids also affect dendritic cell function, promoting their maturation, survival, migration, and mobility (**E**), and at the same time affecting their ability to activate T cells by inhibiting proinflammatory molecule production (**F**). Steroids also act on T helper (Th) cells, including the decrease of transcriptional activity of Th1 cells, and inhibit the production of proinflammatory molecules such as IL-2 and IFNγ (**G**). They also suppress the activity of the GATA3 gene in Th2 cells, inhibiting IL-4 and IL-5 expression (**H**). The action of steroids on Th17 cells (**I**) and regulatory T lymphocytes in not well understood (**J**)

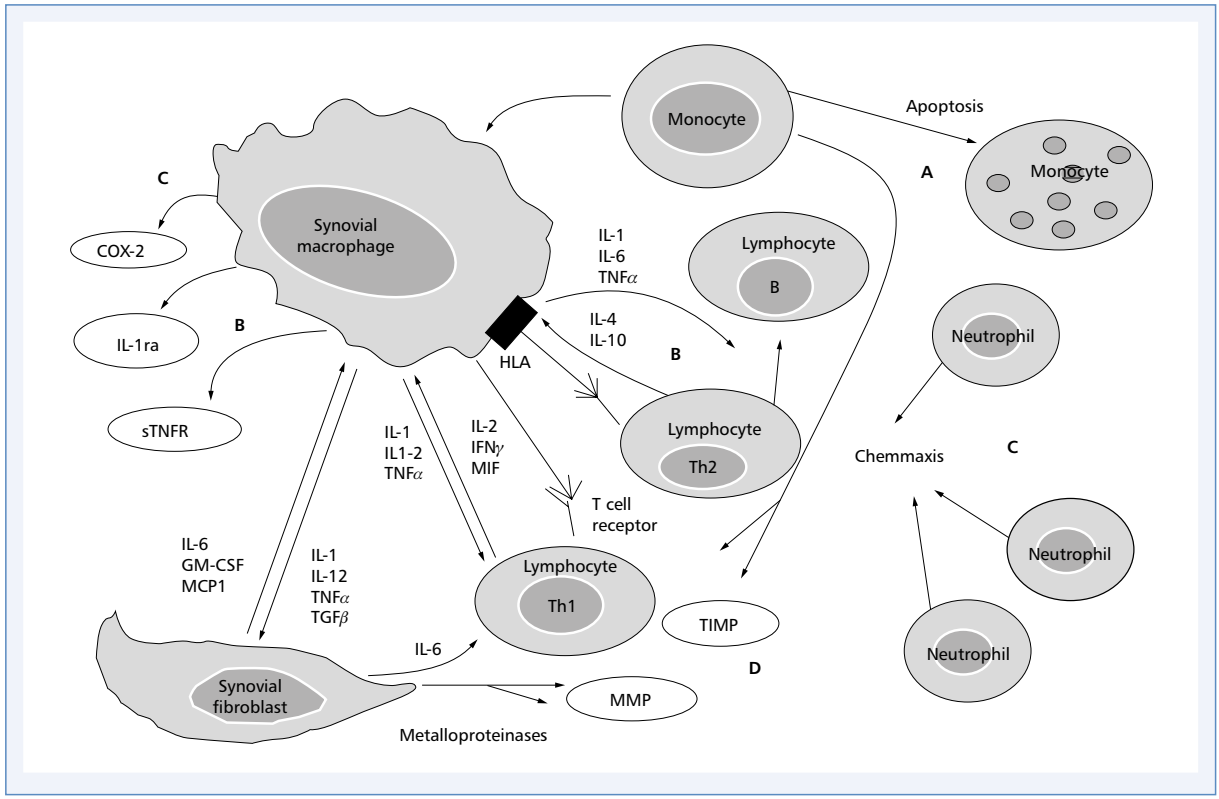

Figure 7B. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — effect of methotrexate on cells of the immune system [28]. (**A**) MTX inhibits monocyte growth and increases their apoptosis. (**B**) MTX decreases IL1 and IL6 secretion and increases IL-1ra production. At the same time, MTX increases the expression of the IL-4 and IL-10 genes and decreases the expression of pro-inflammatory cytokine genes Th1 (IL-2 and IFNγ). (**C**) MTX inhibits COX-2 synthesis and neutrophil chemotaxis, which is dependent on it. (**D**) MTX indirectly inhibits (via cytokine modulation) metalloproteinase production. MTX — methotrexate; IL-1ra — interleukin-1 receptor antagonist; IFNγ — interferon γ; COX-2 — cyclo-oxygenase-2; MMP — metalloproteinase; TIMP — tissue inhibitor of metalloproteinase

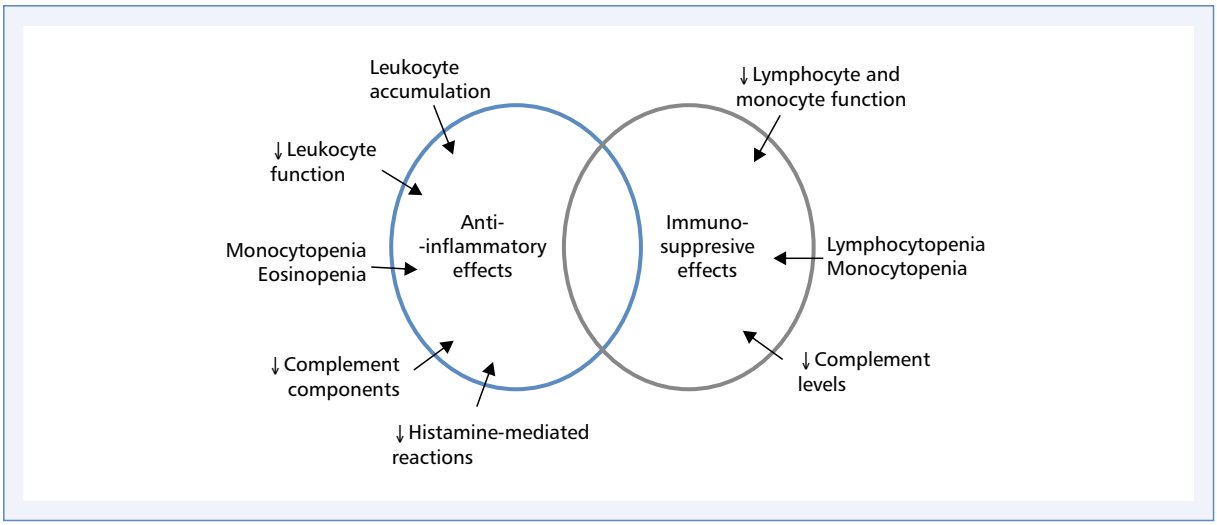

Figure 7C. Immunological basis for the lack of effects of immunotherapy in patients treated by immunosuppression — the physiological effect [29]

with diagnosis of such diseases as Crohn's disease, multiple sclerosis, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, scleroderma, and ulcerative colitis.

At present, on the basis of available data, we conclude that an autoimmune disease is not an absolute contraindication for immunotherapy if strict clinical monitoring of the patients and a specialist consultation (e.g. rheumatologist, dermatologist) are ensured. We would, however, hesitate to offer this therapy in adjuvant treatment. In the case of patients with more severe autoimmune diseases (e.g. Guillain-Barré syndrome) one should be aware of the high risk of potential life-threatening complications and inform the patient. Patients with severe autoimmune diseases treated with biological drugs or who have life-threatening autoimmune disease complications (e.g. severe Crohn's disease) in their medical history should not be qualified for immunotherapy, in contrast to patients with minimal-symptom autoimmune disease (e.g. mild skin psoriasis). The qualification should be preceded by a conversation with the patient including discussing the consequences of an exacerbation of the autoimmune disease.

Summary

The blocking of immunological checkpoints dependent on CTLA-4 and PD-1 is an effective strategy of treating patients with a histologically confirmed diagnosis of skin or mucous membrane melanoma in stage III (non-resectable) or IV regardless of the status of the *BRAF* gene mutation. Immunotherapy can be considered already in the first-line treatment of all patients with melanoma (Figure 2) [3, 23]. The introduction of nivolumab, pembrolizumab, and ipilimumab into clinical practice has allowed an improvement in the prognosis for a large group of melanoma patients (Figure 3, 4). The use of these antibodies has yielded treatment results not observed earlier (Figure 5, 6). Nivolumab and pembrolizumab are better tolerated than ipilimumab because of their relatively low toxicity [5, 13]. Patients treated by immunotherapy when starting their treatment must have satisfactory parameters of morphology and blood biochemistry including the number of leucocytes $\geq 2000/\mu L$, the number of neutral granulocytes $\geq 1000/\mu L$, the number of platelets $\geq 75{,}000/\mu L$, haemoglobin concentration ≥ 9 g/dL or ≥ 5.6 mmol/L, serum creatinine concentration $\leq 1.5 \times$ GGN, AST/ALT activity $\leq 2.5 \times$ GGN, and total bilirubin concentration $\leq 1.5 \times$ GGN or direct bilirubin $\leq$ GGN in patients with total bilirubin levels > 1.5 GGN. At the same time, as is shown by analyses, immunotherapy with checkpoint inhibitors has similar effectiveness and toxicity in persons aged ≥ 65 years and < 65 years, and chronological age by itself should not exclude the use of these drugs [33]. Qualification for immunotherapy, however, has some limitations and contraindications due to its mechanism of action (Figure 1), and these are pre-existing active autoimmune diseases including Crohn's disease or multiple sclerosis, as well as the patient taking systemic immunosuppressive therapy based on corticosteroids and/or methotrexate (Figure 7) or immunosuppressive biological drugs [13]. Currently patients who have received live vaccines, with immune deficiency, active HIV infection, or another active infection including active tuberculosis are not qualified for immunotherapy. Infections with hepatitis B virus, hepatitis C virus, and HIV were almost universal exclusion criteria in investigations of immunological checkpoint inhibitors. It seems that these chronic infections could suppress T cell function and theoretically could decrease the effectiveness (particularly in the case of severe HIV/AIDS with a low number of CD4 + T cells) [34]. The principles of procedures for patients with a diagnosis of melanoma with metastases to the CNS have been described in the paper "Management of brain metastases in melanoma" (Piotr Rutkowski, Dorota Kiprian, Monika Dudzisz-Śledź, Tomasz Świtaj, Radosław Michalik, Mateusz Spałek, Katarzyna Kozak, Tomasz Mandat) [35], similarly to the principles of action in the case of combining immunotherapy with radiotherapy "The role of radiotherapy in melanoma" (Mateusz Spałek, Anna M. Czarnecka), which was also presented in "Oncology in Clinical Practice" [36].

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