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Review article

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Combined or sequential treatment of advanced melanoma?

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Melanoma is a malignant neoplasm with a very high rate of growth in the number of cases. In Poland, in the years 1980–2010, the number of cases of melanoma increased threefold. Although the incidence rates of melanoma are rising, the mortality rate due to melanoma is falling. In recent years, the treatment of patients with melanoma has changed to a great extent. Thanks to the development of molecular research, the presence of specific mutations in melanoma cells was discovered. The progress in understanding the molecular mechanisms occurring in this neoplastic cells and the interaction between the immune system cells and melanoma cells contributed to the development of new classes of drugs: immunotherapy and targeted therapy.

With the use of checkpoint inhibitors, long-term remission of the disease can be achieved, which has been confirmed in many clinical trials that have shown improvements in overall survival (OS) and progression free survival (PSF). However, the predominant problem is the low response rate to checkpoint inhibitors and the time between the initiation of therapy and the response to treatment. This is not the case with targeted therapies, where the response rate is high and the response time is very short. Therefore, a promising treatment strategy can be a combination of these two classes of drugs, so that one can try to achieve a quick and long-term response to the treatment. The paper discusses the current treatment options for melanoma patients in the spreading phase of the disease and analyzes the benefits of combined and sequential treatment.

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Key words: melanoma, immunotherapy, targeted therapy, sequential treatment

Introduction

Melanoma is a malignant neoplasm with a very high rate of growth in the number of cases. In Poland, in the years 1980–2010, the number of cases of melanoma increased threefold [1, 2]. Although the incidence rates of melanoma are rising, the mortality rate due to melanoma is falling. Low grade melanoma has a very good prognosis and is usually completely curable with surgical methods, while 5-years survival rate reaches as much as 99%. However, melanomas with metastases to regional lymph nodes or distant metastases are characterized by much worse prognosis: 5-year survival rates are 63% and 20% respectively [3]. Despite significant progress, the prognosis of patients with melanoma in the spreading phase of the disease is still unsatisfactory and new treatment strategies are constantly being sought.

In recent years, the treatment of patients with melanoma has changed to a great extent. Thanks to the development of molecular research, the presence of specific mutations in melanoma cells was discovered. It is estimated that melanoma cells show *BRAF* V600 mutation in about 50% of patients with disseminated melanoma [4]. The progress in understanding the molecular mechanisms occurring in melanoma cells and the interaction between the immune system cells and melanoma cells contributed to the development of new classes of drugs: immunotherapy and targeted therapy. Immunotherapy is based on immune checkpoint inhibitors (ICIs), which inc-

lude anti-cytotoxic T-lymphocyte antigen 4 antibodies (anti--CTLA-4) and anti-programmed death receptor-1/ligand-1 (anti-PD-1/anti-PD-L1) antibodies. The first registered ICI drug was ipilimumab (anti-CTLA-4), followed by nivolumab and pembrolizumab (anti-PD-1). Another group of drugs is targeted therapy, which includes BRAF inhibitors (BRAFi; vemurafenib, dabrafenib and encorafenib) and MEK inhibitors (MEKi; cobimetinib, trametinib, binimetinib). It is also worth mentioning the introduction of oncolytic talimogene laherparepvec virus (T-VEC) to the treatment of patients with melanoma.

With the use of checkpoint inhibitors, long-term remission of the disease can be achieved, which has been confirmed in many clinical trials that have shown improvements in overall survival (OS) and progression free survival (PSF). However, the predominant problem is the low response rate to checkpoint inhibitors and the time between the initiation of therapy and the response to treatment. This is not the case with targeted therapies, where the response rate is high and the response time is very short. Therefore, a promising treatment strategy can be a combination of these two classes of drugs, so that one can try to achieve a quick and long-term response to the treatment. The paper discusses the current treatment options for melanoma patients in the spreading phase of the disease and analyzes the benefits of combined and sequential treatment.

Immunotherapy

Anti-CTLA-4 or anti-PD-1 monotherapy

Ipilimumab

Ipilimumab is a recombinant human monoclonal antibody, IgG1 subclass, with a half-life of 12–14 days, binding to the CTLA-4 (CD152) molecule [14]. By blocking CTLA-4, the anti-neoplastic immune response is activated. Three phase II studies – CA184-022, CA184-008 and CA184-007 [5–7] – using ipilimumab in monotherapy in patients with advanced melanoma showed a median survival rate of 8.6–11.0 months and a percentage of 1-year survival rate of 39–48%. Subsequent analyses showed a 2-year survival rate of 30% [8] and a 3-year survival rate of 25% at the dose of 10 mg/kg of body weight. [9]. However, there is no data available to indicate that this drug leads to permanent cures in melanoma patients. In 2010, the results of the phase III study (MDX010-20) using ipilimumab in patients with advanced melanoma were presented [10]. The median survival time of patients treated with ipilimumab was 10.0 months, of patients treated with ipilimumab and gp100 – 10.1 months and in both cases it was significantly higher than in the control group (median survival time: 6.4 months). In 2011, in a study evaluating the efficacy of ipilimumab at the dose of 10 mg/kg of body weight (in combination with dacarbazine) in the first-line therapy, long-term responses were demonstrated in some patients and an improvement in total survival rate (the percentage of 2-year OS was 28.5%) [11, 12]. The analysis of 12 clinical trials confirmed the potential long--term effect of ipilimumab on the survival rate, and the 10-year survival curve reached a plateau at about 20% [13]. However, ipilimumab is not currently used in monotherapy as first-line option treatment.

Nivolumab and pembrolizumab

Nivolumab has a structure of a human monoclonal IgG4 antibody with a half-life of approximately 26 days and is specific to the PD-1 receptor. The mechanism of action of both nivolumab and pembrolizumab is to bind the drug to the PD-1 receptor and block the interaction with PD-L1 and PD-L2 ligands, which in turn activates T-lymphocytes for an immune response against neoplastic cells [14]. Two large phase III studies, CheckMate-066 [15] and CheckMate-037 [16], confirmed the efficacy of nivolumab in the treatment of melanoma patients. In the CheckMate-066 study, nivolumab was used as the first-line treatment in patients without *BRAF* mutations. The comparator in the study was dacarbazine. The percentage of 2-year-old OS for nivolumab was 57.7% and PSF 39.2% [17], the percentage of 3-year-old OS was 51.2% and PFS 21.6%. The number of objective responses to nivolumab was 40% and to dacarbazine it was 13.9% [18]. The OS median for nivolumab was 37.5 months and 11.2 months for dacarbazine. In turn the median PFS was 5.1 and 2.2 months respectively [15, 18]. In the CheckMate-037 study, nivolumab was used as a follow-up treatment in patients after ipilimumab and BRAFi if a mutation was found in the *BRAF* gene. Dacarbazine or paclitaxel with carboplatin were used as comparators. The median OS in this study was 16 months for nivolumab and 14 months for chemotherapy and the median PFS: 3.1 and 3.7 months, respectively; objective responses were obtained in 27% and 10% patients, respectively [19].

Pembrolizumab is a humanized monoclonal IgG4 antibody with a half-life of about 27 days [20]. Its efficacy was confirmed in phase III KEYNOTE-006 study, with the participation of patients with advanced melanoma, who had not been previously taken part in systemic treatment. Patients were assigned to 3 groups of patients receiving pembrolizumab every 2 or 3 weeks or ipilimumab [21]. The median OS was 32.7 months in groups treated with pembrolizumab and 15.9 months in groups treated with ipilimumab. The median PFS was 8.4 and 3.4 months respectively [22, 23]. Objective responses were obtained in the group receiving pembrolizumab every 2 or 3 weeks in 33.7% and 32.9% of patients respectively, and in the group treated with ipilimumab in 11.9% [21].

Combination therapy using anti-CTLA-4 with anti-PD-1

The first attempts to combine CTLA-4 and PD-1 inhibitors were made in phase I, where the combination of nivolumab at a dose of 1 mg/kg of body weight with ipilimumab at a dose of 3 mg/kg of body weight was tested [24]. The basic study that evaluated the efficacy of combination therapy: nivolumab with ipilimumab was the phase III study CheckMate-067 [25]. The

median OS was not obtained in the group receiving nivolumab with ipilimumab, in the group with nivolumab it was 36.9 months, and in the group with ipilimumab 19.9 months. The median PFS reached 11.5 months, 6.9 months and 2.9 months respectively, with objective responses of 57.6%, 43.7% and 19% respectively. It should be noted that the combination of nivolumab with ipilimumab gave better results in patients with low expression of PD-L1 in melanoma tissue (<5%). In case of high expression of PD-L1 in melanoma tissue, the treatment results for monotherapy with nivolumab and combined therapy with PFS and OS were similar [25]. Adverse events related to treatment in grade 3 and 4 have been reported:

- in the group receiving nivolumab with ipilimumab – in 185 (59%) out of 313 patients,
- in the group receiving nivolumab – in 70 (22%) out of 313 patients,
- in the group receiving ipilimumab – in 86 (28%) out of 311 patients [26, 27].

Another study that evaluated the association of anti-CTLA-4 with anti-PD-1 was the III/IV phase of CheckMate-511 study [28]. It compared 2 different doses of both drugs, i.e. nivolumab at a dose of 1 mg/kg of body weight with ipilimumab at a dose of 3 mg/kg of body weight (NIVO1+IPI3) and nivolumab at a dose of 3 mg/kg of body weight with ipilimumabat a dose of 1 mg/kg of body weight. (NIVO3+IPI1). Objective response to treatment was obtained in 45.6% of cases in the NIVO3+IPI1 group and 50.6% in the NIVO1+IPI3 group, and the percentage of complete remissions – (CR) was 15.0% and 13.5% respectively. The median OS was not obtained in any of the groups and the median PFS was 9.9 months in the NIVO3+IPI1 group and 8.9 months in the NIVO1+IPI3 group. Annual PFS was 47.2% and 46.4% respectively and annual OS was 79.7% and 81% respectively.

The association of pembrolizumab at a dose of 2 mg/kg of body weight with ipilimumab at a low dose of 1 mg/kg of body weight at the phase Ib of KEYNOTE-029 study was also evaluated. The number of objective responses to treatment was 61%, including 15% of CR. In 27% of treated patients adverse effects were reported in grades 3 and 4 [29, 30].

Targeted therapy

Monotherapy with BRAF orMEK inhibitors

Vemurafenib

Vemurafenib is a low molecular weight BRAF serine threonine kinase inhibitor used in melanoma patients with mutations in the *BRAF* gene [31]. In phase III of the BRIM-3 study, vemurafenib and dacarbazine were compared in patients with advanced melanoma, who had not previously undergone systemic treatment, with the presence of mutations in the *BRAF V600E* gene [32]. The median OS in the group receiving vemurafenib was 13.6 months and in the group with dacarbazine – 9.7 months in the analysis before cross-over to vemurafenib (in the analysis after cross-over the median OS was 10.3 months). The median PFS was 6.9 and 1.6 months respectively [32, 33]. The 1-, 2-, 3- and 4-year survival rate constituted 56% and 46%, 30% and 24%, 21% and 19%, as well as 17% and 16%, respectively. In the group receiving vemurafenib, 48% of responses to treatment were reported, and in the group treated with dacarbazine – 5% [32].

Dabrafenib

Dabrafenib is a reversible BRAF V600 kinase inhibitor used in melanoma patients with mutations in the *BRAF* gene. In the BREAK-3 study, dabrafenib was compared with dacarbazine in patients with advanced melanoma with the present *BRAF* V600E mutation who had not received previous systemic treatment. Because of the planned cross-over to dabrafenib after disease progression, the primary endpoint was PFS, which in the group with dabrafenib was 5.1 months and in the group with dacarbazine – 2.7 months [34]. According to data presented at the ASCO conference in 2013, the median OS in the dabrafenib-treated group was 18.2 months and in the dacarbazine-treated group 15.6 months, while the number of responses to dabrafenib treatment was 59% [17].

Encorafenib

Encorafenib, like dabrafenib and vemurafenib, it is an inhibitor of BRAF V600 kinase. However, it differs from them by 10 times longer half-life of dissociation (>30 h). This probably results in higher antineoplastic activity and at the same time less activation of the MAPK pathway in healthy tissues, which is responsible for the development of adverse effects [37]. The combination of encorafenib with binimetinib compared to encorafenib or vemurafenib was evaluated in the COLUMBUS study [43, 44].

Trametinib

Trametinib is an oral, low-molecular, selective inhibitor of MEK1 and MEK2 kinase. Trametinib was evaluated in phase III of the METRIC study and compared with chemotherapy (dacarbazine or paclitaxel) in patients with advanced melanoma with *BRAF* V600E/K mutation [35]. In this study, the median PFS was 4.9 months for trametinib and 1.5 months for chemotherapy, and 1-, 2-, 5-year total survival for trametinib and chemotherapy was 60.9% and 49.6%, 32.0% and 29.4%, 13.3% and 17.0% respectively. In the vast majority of patients at the early stage of treatment, a cross-over (n = 70, 65%) to trametinib was used [36].

Binimetinib

Binimetinib, just as trametinib, is an oral, low-molecular, selective inhibitor of MEK1 and MEK2 kinase. Its efficacy was assessed in a phase III study with NEMO randomization, where it was compared with dacarbazine in patients with advanced melanoma with *NRAS* mutation. The median OS in the group receiving binimetinib was 11 months, and in the group receiving dacarbazine – 10.1 months. The median PFS was 2.8 and 1.5 months respectively, and the rate of responses was 15% and 7% respectively [38].

Therapy combined with BRAF and MEK inhibitors

Vemurafenib with cobimetinib

The efficacy of the combination of vemurafenib and cobimetinib was confirmed by phase III of coBRIM study [39]. It showed the advantage of combination of vemurafenib and cobimetinib over monotherapy with vemurafenib. The median OS and PFS for the combination was 22.3 and 12.3 months for the combination and 12.3 and 7.3 months for the vemurafenib respectively. Similarly, the number of objective responses for vemurafenib with comimetinib was 70% and 50% respectively. One of the advantages of using the combination in comparison with monotherapy with BRAF inhibitor was significantly lower number of skin complications.

Dabrafenib with trametinib

The combination of dabrafenib and trametinib was evaluated in two studies of the third phase of COMBI-d [40] and COMBI-v [41]. In the first one, dabrafenib with trametinib was compared to dabrafenib and in the second one to vemurafenib. The median OS in COMBI-d was 25.1 months for the combination and 18.7 months for the trametinib, the median PFS was 11 and 8.8 months respectively, while the number of objective responses to treatment ranged from 69% to 53%. In the COMBI-v study, the median OS for the combination was 25.6 months and for vemurafenib 18 months, while the median PFS was 11.4 and 7.3 months, respectively, and the number of responses to treatment was 64% and 51%. The updated 5-year follow-ups in COMBI-d and COMBI-v showed a 4-year PFS of 21% and a 5-year PFS of 19%. Four-year OS was 37% and five-year OS was 34%. Total remission was observed in 19% of patients with 5-year-old OS at 71% [42].

Encorafenib with binimetinib

The efficacy of the combination of encorafenib and binimetinib was evaluated in the COLUMBUS study [43, 44]. Encorafenib and binimetinib were compared with encorafenib or vemurafenib. The OS median for the combination was 33.6 months and 16.9 months for vemurafenib. The median PFS for encorafenib with binimetinib was 14.9 months, for encorafenib 9.6 months and for vemurafenib 7.3 months. However, the number of objective responses to treatment was 64%, 52% and 41% respectively.

Immunotherapy with targeted therapy

Combinations of immunotherapy and targeted therapy are currently being tested in many clinical trials. This treatment is used in patients with melanoma with the current mutation in the *BRAF* gene. This combination of therapies seems very promising. It enables a significant number of responses to be obtained in a short time using BRAFi/MEKi and a long-term maintenance of these responses during treatment with checkpoint inhibitors. Another justification for this management strategy is based on different mechanisms of action of individual therapies, which, due to their complementary action, may improve the effects of treatment [45].

The first combinations of targeted therapies with immunotherapy for melanoma referred to ipilimumab and vemurafenib. However, the study was discontinued due to significant hepatotoxicity of combined therapy [46]. Subsequent studies concerned the combination of ipilimumab or nivolumab or pembrolizumab with dabrafenib and trametinib [47]. The first results of treatment with pembrolizumab, dabrafenib and trametinib are promising, with PFS of 16 months and 59.8% response rates with a median response time of 18.7 months and acceptable treatment toxicity [47]. The study evaluating the toxicity of the combination of atezolizumab, vemurafenib and cobimetinib resulted in 71.8% objective responses and 39.3% with a median response duration of 17.4 months [48]. Currently, patients with advanced melanoma are undergoing a number of clinical trials to combine targeted therapy with immunotherapy, but most often these are phase I and phase II studies [49]. However, the results of treatment of patients with advanced melanoma are still yet to come, as they require confirmation in subsequent clinical trials.

Strategy of management of patients with advanced melanoma

At present, the following therapies are registered for the treatment of patients with melanoma in inoperable grade III and grade IV:

Combined treatment

a) patients with a present mutation in the *BRAF* gene:
- dabrafenib with trametinib
- encorafenib with binimetinib
- vemurafenib with cobimetinib
- nivolumab with ipilimumab

b) patients with no mutation in the *BRAF* gene:
- nivolumab with ipilimumab (currently not refundable in Poland).

Monotherapy

a) patients with a mutation in the *BRAF* gene:
- dabrafenib
- trametinib
- vemurafenib
- nivolumab
- pembrolizumab
- iplimumab

b) patients with no mutation in the *BRAF* gene:
- nivolumab
- pembrolizumab
- iplimumab.

In the light of current studies, the use of targeted therapies as monotherapy may be justified only in case of significant complications during BRAFi-MEKi combination therapy [39–

44]. However, if complications occur during combined therapy, the combination of BRAFi and MEKi with a different toxicity profile should be considered first. In the case of checkpoint inhibitors, the use of immunotherapy as a monotherapy is preferred in most patients due to its low toxicity. The combination of nivolumab and ipilimumab should be recommended especially in patients with asymptomatic CNS metastases [50–52]. However, the sequence of therapies, especially in patients with the present mutation in the *BRAF* gene, remains a problem.

A very practical solution was proposed in the work by Schvartsman et al. [50]. He distinguished two prognostic groups among patients with melanoma in inoperable grade III and in grade IV: low and high risk (table I). Then, depending on the risk group and the presence or absence of metastases in the CNS, he presented 4 possible scenarios of management (fig. 1–4):

- low-risk patients without metastases in CNS;
- low-risk patients with metastases in CNS;
- high-risk patients without metastases in CNS;
- high-risk patients with metastases in CNS.

Such a division can be very useful in everyday medical practice. It seems that if the patient is in good general condition, the tumor mass is small and occurs in 1–2 locations and the LDH level is normal or slightly elevated, the best option is to start therapy with checkpoint inhibitors. Of course, attention should be paid to possible contraindications to immunotherapy and a discussion with the patient about other available therapeutic options.

In situations where the disease is rapidly progressing and a mutation is present in the *BRAF* gene, BRAFi and MEKi are the therapies of choice (in some cases checkpoint inhibitors may also be considered). One can also optionally start treatment with BRAFi and MEKi (for a short period of time) to stop the neoplastic process and then move on to immunotherapy. However, new therapeutic options and drug combinations are being sought to achieve long-term survival in this group of patients.

Table I. Prognostic groups of patients according to Schvartsman et al. [50]

Factor/group	Low-risk group	High-risk group
Tumor mass size (total volume)	<10 cm	≥10 cm
Number of locations where metastases were found	<3 locations	≥3 locations
LDH concentration value	Normal	≥2 × upper limit of normal
Performance status	0 or 1	≥2

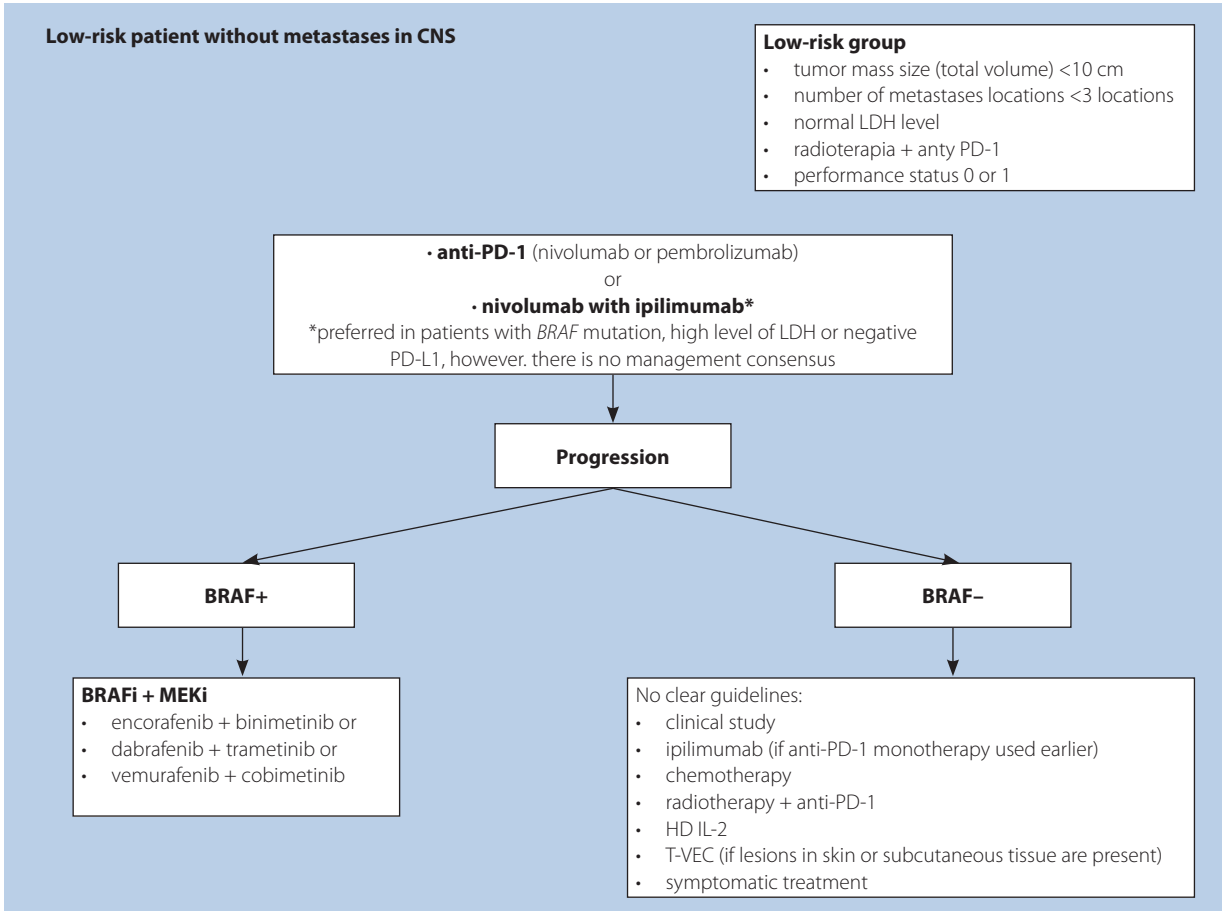

Figure 1. Management algorithm 1. Low-risk patient without metastases in CNS

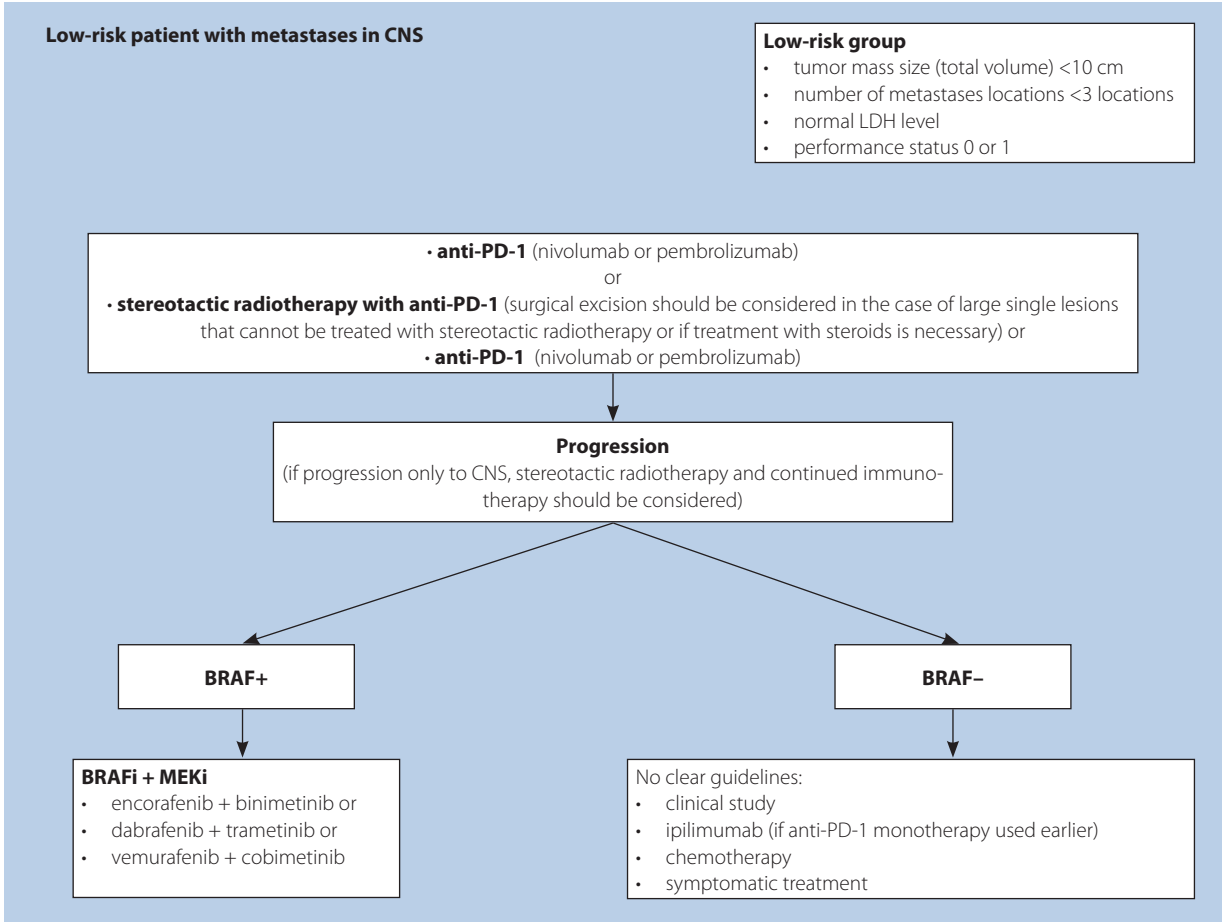

Figure 2. Management algorithm 2. Low-risk patient with metastases in CNS

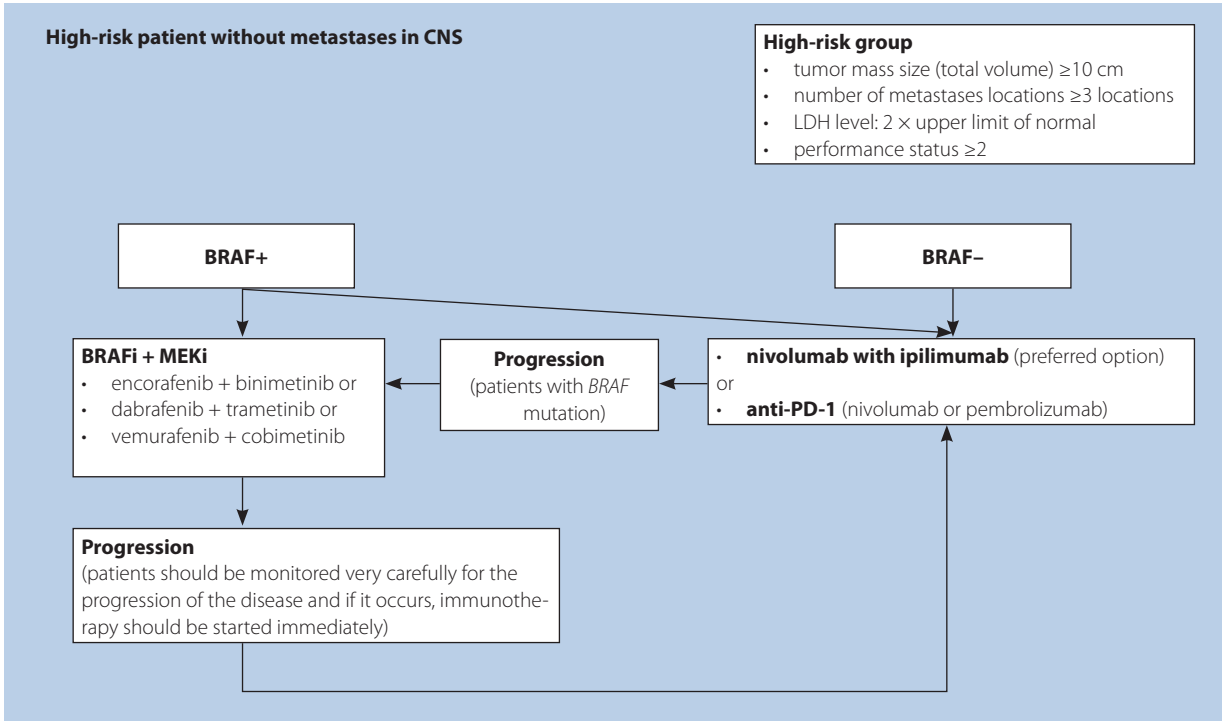

Figure 3. Management algorithm 3. High-risk patient without metastases in CNS

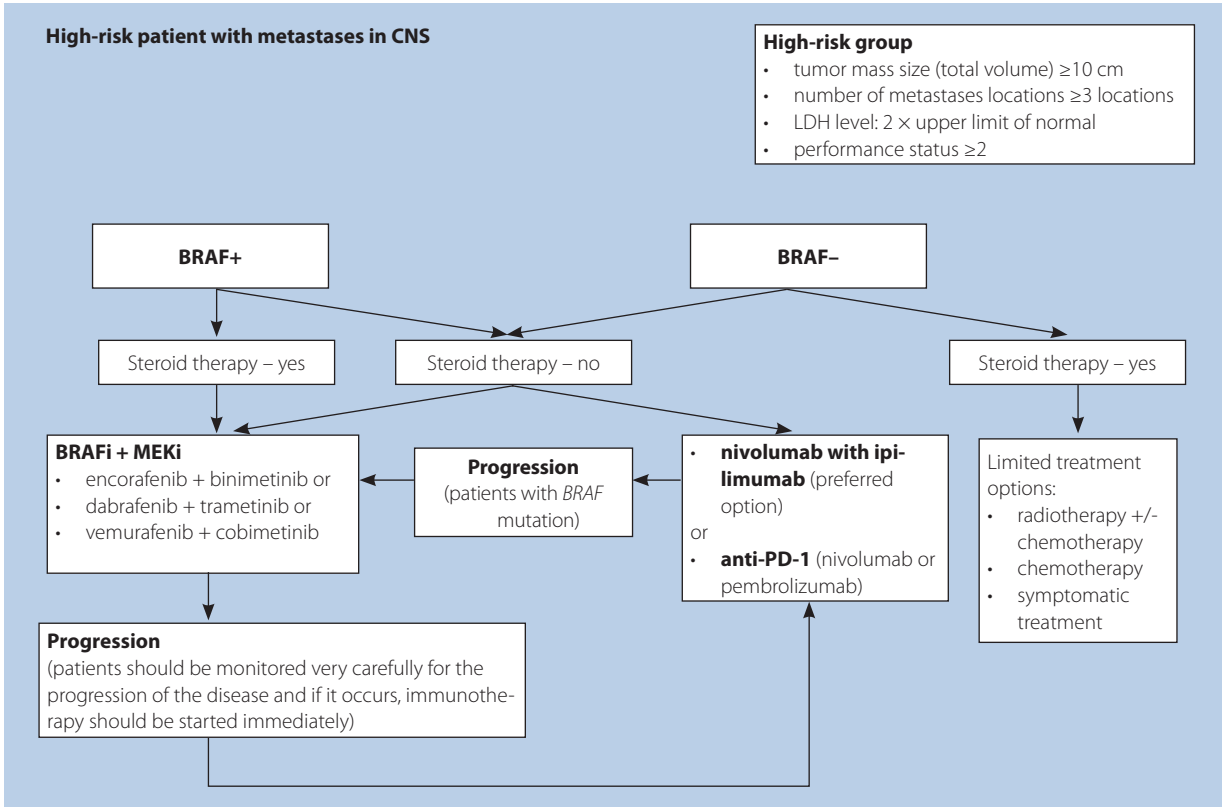

Figure 4. Management algorithm 4. High-risk patient with metastases in CNS

Summary

The emergence of new therapies has certainly improved the survival rates of melanoma patients. However, there is still a group of patients in whom the efficacy of the treatment is unsatisfactory and further research is needed to answer the question: "Why do these patients not respond to the treatment applied?". Other problems have also emerged in relation to the toxicity of new drugs and the sequence and duration of treatment, which require further research.

Conflicts of interest: Bożena Cybulska-Stopa: lectures, analyses, conferences sponsored by BMS, MSD, ROCH, Novartis, Pierre Fabre.

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