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Management of melanoma central nervous system metastases

Introduction

Melanoma is the third most frequent malignancy (after breast and lung cancers) that causes metastases in the central nervous system (CNS). It is one of the 20 most common human cancers, and its incidence is steadily increasing by about 3–7% per year. It is estimated that in about 50–60% of patients with advanced melanoma, the disease will disseminate in the CNS (of whom about 75% of patients will develop multiple metastases often asymptomatic at baseline). Central nervous system metastases are found in 7% of melanoma patients at diagnosis and about 75% on autopsy. The primary tumor cannot be found in 3% of patients diagnosed with melanoma metastasis in the CNS. Of note is that only 8–46% of melanoma patients are diagnosed with CNS metastases. In 94% of them, brain metastases are the direct cause of death. In the latest 8th edition of the American Joint Committee on Cancer (AJCC) staging system, the presence of CNS metastases was distinguished as a separate, last category in stage IV (M1d) [1]. The risk of metastases in the CNS increases with the disease stage [2]. Central nervous system metastases occur in 37% of patients with stage IV melanoma [3]. Currently, there are no known factors identified that predict the risk of CNS metastases in melanoma patients. Nevertheless, it is known that certain factors are associated with a higher risk of metastases in the CNS (primary lesion within the head and neck, elevated lactate dehydrogenase (LDH) activity, ulceration in the primary lesion, mutations in the *BRAF*, *NRAS,* and *PTEN* genes) [4]. The detection of lesions in the CNS is associated with poor prognosis. Central nervous system metastases lead to death in 20–50% of patients, and symptomatic lesions are the immediate cause of death in about 90% of patients. According to historical data, median overall survival (OS) after CNS metastasis diagnosis was 5 to 7 months. However, in symptomatic patients undergoing whole brain radiotherapy (WBRT), which is now rarely used, median OS was 2–5 months, and in patients undergoing surgery or stereotactic radiotherapy — twice as long [5].

This summary study aims to present multidisciplinary guidelines on diagnostic and therapeutic management of melanoma patients with CNS metastases, which is currently the greatest challenge in the care of patients with advanced melanoma.

New treatment methods introduced into daily clinical practice have resulted in a significant change in therapeutic management compared to those used 5 years ago. Central nervous system metastases are increasingly diagnosed at the asymptomatic stage using routine magnetic resonance imaging (MRI) and/or computed tomography (CT) of the brain as part of the follow-up or qualification of patients for systemic treatment. Advanced techniques of stereotactic radiotherapy have become the main therapeutic option used in local treatment. In the last 10 years, 11 new drugs for patients with advanced melanoma have been registered in Europe [vemurafenib, dabrafenib, trametinib, cobimetinib,

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binimetinib, encorafenib, ipilimumab, nivolumab, pembrolizumab and relatlimab in combination with nivolumab and talimogene laherparepvec (T-VEC)]. In Poland, 6 of the new therapies are currently available under drug programs (vemurafenib with cobimetinib, dabrafenib with trametinib, encorafenib with binimetinib, ipilimumab with nivolumab, pembrolizumab, and nivolumab). Based on data from clinical trials median OS in the entire group of patients with *BRAF* mutant metastatic melanoma treated with pembrolizumab/ /nivolumab and a combination of BRAF (BRAFi) and MEK (MEKi) inhibitors is now approximately 2 years (approximately 4 times longer than 5 years ago). So far, the best results have been achieved with dual immunotherapy (anti-CTLA-4 and anti-PD-1). The combination of anti-PD-L1 therapy with BRAFi and MEKi (e.g. atezolizumab plus vemurafenib and cobimetinib) also allows for obtaining some benefits. Perhaps using other methods of combined treatment, for example, anti-PD-1/anti-PD-L1 with anti-LAG3 and/or TIM3 will allow further improvement. In each case of confirmed CNS metastases, it is mandatory to examine the status of the *BRAF* gene in the fixed material (if it has not been previously assessed) [6, 7]. According to the current National Comprehensive Cancer Network (NCCN) and European Society of Clinical Oncology (ESMO) guidelines, in patients with *BRAF*-mutated melanoma and metastases in the CNS (especially asymptomatic and less than 3 cm in size), dual immunotherapy is recommended if no contraindicated. However, depending on the clinical setting, the use of BRAFi and MEKi in the first line of treatment should be considered.

Even in the treatment of multiple metastatic lesions, the use of modern radiotherapy techniques has become much more common, replacing WBRT in many clinical situations. Stereotactic radiotherapy involves delivering a biologically high dose of radiation to a precisely defined small volume with a significant decrease in the dispersed dose in healthy tissues outside the target volume. Treatment can be done with a single fractional dose [stereotactic radiosurgery (SRS)] or 3–5 fractions (fractionated stereotactic radiosurgery, fSRS).

Therapeutic decisions should be individualized, taking into consideration treatment goals (short-term *versus* long-term benefits) and based on clinical picture (LDH level, other organs involvement, tumor mass, patient performance status, course of the disease, comorbidities and their treatment, and patient preferences) [8]. The basic and applicable rule in the case of melanoma metastases in the CNS should be optimizing the management by multidisciplinary teams whose members are experienced in the diagnosis and treatment of patients with melanoma. The team should include at least a neurosurgeon, a radiation oncologist, and a clinical oncologist [9].

Diagnostics

Signs and symptoms of CNS metastases may be mild and difficult to recognize. They depend, among other things, on the number, size, and location of metastases. Metastases most often occur in the telencephalon; in about 15% of cases they occur in the cerebrum and about 5% in the brainstem. The most common symptoms include headache (sometimes accompanied by nausea and/or vomiting), seizures, speech, comprehension, and vision disorders, numbness, and movement disorders. The presence of clinical symptoms of CNS metastases is associated with poorer treatment outcomes. Patients with stages I and II melanoma have a lower risk of developing metastases in the CNS compared to patients with stages III and IV [10]. In younger patients, the risk of late metastases in the CNS is higher in thicker melanomas [11]. Based on the data from a retrospective analysis of the large multicenter S0008 study, the risk of CNS metastases at stage IIIB and IIIC was 15%, and metastases were mainly diagnosed within the first 3 years after surgery [12]. The time from treatment of the primary lesion may be relatively long and may even be 3–4 years (median) [13].

Therefore, in patients with stage III and IV melanoma, the detection of CNS metastases based on follow-up imaging tests in the absence of clinical symptoms is of great importance. The prognosis in asymptomatic patients and the efficacy of treatment are definitely better compared to patients with symptoms resulting from CNS metastases. The risk of developing CNS metastses in patients with stage IV melanoma is very high and reaches almost 40%. Performing an MRI of the CNS during the disease staging after the diagnosis of stage IV melanoma is the standard of care. In stage III, the risk of developing metastases in the CNS is also high and ranges from 18.5 to 23.5% [14, 15]. In asymptomatic patients with melanoma stage IIIC and higher, CT or MRI of the CNS should be considered [7]. The results of the analysis of 202 patients done by Derks et al. indicate that routine MRI in patients after radical resection of stage III melanoma before starting adjuvant treatment is not recommended [3, 16]. Performing periodic MRI examinations for up to 3 years after treatment cessation is indicated to detect asymptomatic CNS metastases (especially in high-risk patients — i.e. stage IIIC or higher, in whom no CNS metastases have been detected so far). Patients with successful treatment of CNS metastases in the past require regular follow-up with MRI. In patients with signs and/or symptoms (including even mild symptoms) indicating the possibility of CNS lesions, an MRI examination is recommended [17]. MRI is the most sensitive imaging for detecting CNS metastases and has an advantage over contrast-enhanced CT. It should be emphasized

Table 1. Recursive Partitioning Analysis (RPA) prognostic scale (n = 1200) [19]

	Class I	Class II	Class III
KPS [points]	≥ 70	≥ 70	< 70
Primary tumor	Cured	Active	Active
Age	< 65 years	> 65 years	Any
Non-CNS lesions	No	Present	Present
Prevalence	15%	65%	20%
Median survival [months]	7.1	4.2	2.3

CNS — central nervous system; KPS — Karnofsky performance status

Table 2. Prognostic assessment of survival in melanoma patients with brain metastases: Diagnosis Specific — Graded Prognostic Assessment (DS-GPA) scale [20]

KPS [points]	< 70	70–80	90–100	
Number of CNS metastases	> 3	2–3	1	
Points		1	2	
Based on the sum of points assigned according to KPS and the number of metastases				
DS-GPA	0–1.0	1.5–2.0	2.5–3.0	3.5–4.0
Median survival [months]	3.4	4.7	8.8	13.2

CNS — central nervous system; KPS — Karnofsky performance status

that melanoma CNS metastases are usually multifocal and hemorrhagic [18].

Therapeutic management

Therapeutic management depends on the clinical setting and includes systemic, local (radiotherapy and/or surgery), and/or symptomatic treatment. In addition to clinical symptoms, there are numerous disease- and patient-related parameters playing an important role in the treatment of melanoma patients with CNS metastases (number, size, and location of metastases, presence and control of lesions outside the CNS, previous treatment for melanoma and the outcome, *BRAF* gene mutation status, general condition, and age, comorbidities and their treatment). In symptomatic treatment, anti-edematous drugs (mainly glucocorticosteroids) are used. In the case of seizure, antiepileptic treatment should be initiated, but interactions with other drugs used by the patient (including glucocorticoids) should be taken into consideration.

Tables 1 [19] and 2 [20] present prognostic scales in patients with CNS metastases; Recursive Partitioning Analysis — Radiation Therapy Oncology Group (RPA-RTOG) scale applies to all cancers, and Diagnosis Specific — Graded Prognostic Assessment (DS-GPA) scale applies only to patients with melanoma. However, it should be remembered that the aforementioned scales were developed before the introduction of new methods of systemic treatment of patients with metastatic melanomas. The median OS in all melanoma patients

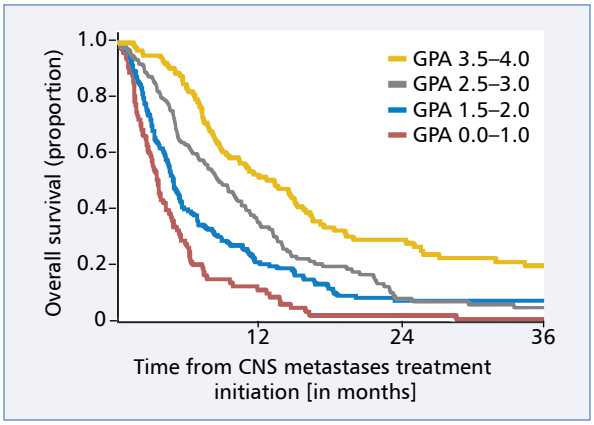

Figure 1. Kaplan-Meier survival curves for individual groups in the Graded Prognostic Assessment (GPA) scale [20]; CNS — central nervous system

was 6.74 months (range: 3.38 to 13.32 months, number of patients n = 481) (Fig. 1).

The management algorithm in melanoma patients with CNS metastases is presented in Figure 2.

Local treatment of melanoma patients with CNS metastases

The expected survival in untreated melanoma patients with symptomatic CNS metastases is 2–3 months, and only 13% of patients have OS longer than a year (prognosis is more favorable in patients below 65 years of age and performance status > 70 according to

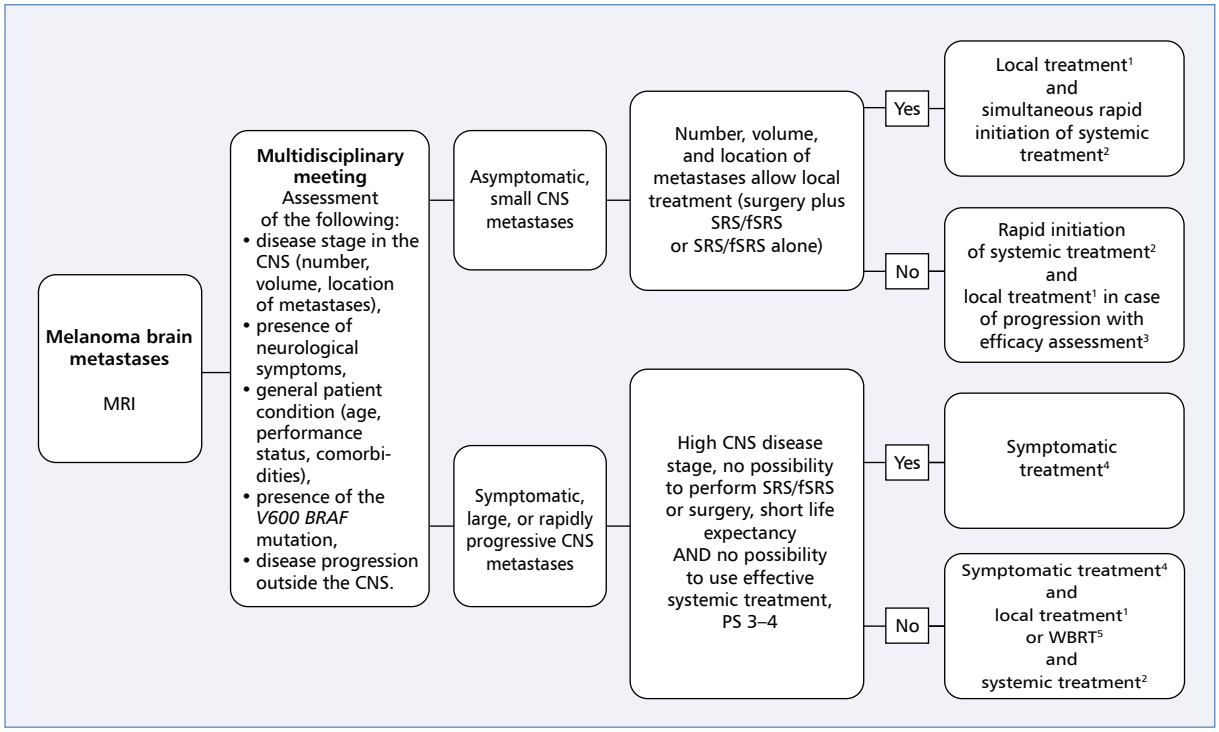

Figure 2. Algorithm of management in melanoma patients with metastases in the central nervous system (CNS); SRS/fSRS — radiosurgery, fractionated radiosurgery (stereotactic radiotherapy); WBRT — whole brain radiotherapy; [1]Local treatment is understood as standalone or combined use of surgical methods and techniques of stereotactic radiotherapy, available options include metastasectomy plus adjuvant SRS/fSRS, hybrid treatment (metastasectomy plus adjuvant SRS/fSRS to postoperative bed plus radical SRS/fSRS of other metastases) or only SRS/fSRS. Hybrid treatment may bring particular benefits in the case of multiple metastases available for SRS/fSRS, among which some lesions give neurological symptoms or are associated with expected lower efficacy of SRS/fSRS (large, bleeding lesions, with a fluid component) and are available for surgical treatment; [2]Available options include immunotherapy (combination of nivolumab with ipilimumab as a combination effective in the CNS) or BRAF inhibitors with MEK inhibitors in patients with a confirmed *BRAF* mutation. The preferred treatment option is dual immunotherapy, regardless of *BRAF* mutation status. In the presence of high-volume disease and clinical symptoms, treatment with BRAF inhibitors with MEK inhibitors in patients with a known *BRAF* mutation should be considered as an alternative. Single-agent immunotherapy does not provide adequate CNS response rates; [3]This management requires close observation of the CNS with the use of contrast-enhanced magnetic resonance imaging (MRI) and comparative assessment. Baseline MRI should be performed at treatment initiation, then in a month, and then every 2–3 months; [4]Anti-oedematous and/or anti-epileptic treatment, if necessary; [5]In the case of leptomeningeal metastases or if SRS/fSRS/metastasectomy is not possible

the Karnofsky scale). Resection or radiotherapy of all metastatic lesions influences the prognosis. In the situation of leaving one of several lesions, the prognosis is identical as in untreated patients [20]. In the case of multiple asymptomatic and non-life-threatening metastases in the CNS, the priority is to start systemic combined treatment with proven value in the CNS (especially — nivolumab and ipilimumab) with the possibility of postponing local treatment until the first assessment of systemic therapy efficacy (especially when WBRT is the only possible procedure due to the multiplicity of metastatic lesions or unavailability of techniques for simultaneous radiotherapy of multiple metastases). In the case of a limited number of metastases available for local treatment techniques, the preferred method of management is a combination of radiotherapy with immunotherapy or molecularly targeted treatment during the first 2–3 months from systemic treatment initiation, instead of radiotherapy as part of salvage treatment [8].

There are still no unequivocal predictors of the occurrence of melanoma metastases in the CNS. However, certain factors are known to be associated with increased risk, including:

— primary lesion within the head and neck;
— increased LDH level;
— ulceration in the primary lesion;
— mutations in the *BRAF*, *NRAS,* and *PTEN* genes [4].

In total 24–58% of patients with CNS metastases have *BRAF* mutation, and 23% of patients have *NRAS* mutation.

Surgical treatment

Eligibility criteria for surgical treatment of melanoma patients with CNS metastases (EBM, 2010, level 1) include:

— newly diagnosed single lesions (up to 4 in total);
— size over 3 cm;
— location of lesions surgically accessible;
— symptomatic lesions:
— lesions causing neurological deficit and/or symptoms of increased intracranial pressure due to their volume and/or associated hemorrhagic focus and/or secondary to fluid tract obstruction leading to hydrocephalus (lesions located in the posterior cranial fossa);
— Karnofsky performance status (KPS) > 70, age < 65 years;
— progression after previous radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) (SRS/fSRS).

The goals of surgical treatment include:
— histological verification;
— radical removal of all lesions, which affects OS (no justification for biopsy); in multiple tumors, it is possible to use hybrid therapy, involving resection of large and surgically accessible lesions in combination with SRS/fSRS for smaller lesions located in deep brain structures;
— improvement or stabilization of neurological status (occurrence of new neurological deficits shortens OS by 4 months);
— enabling further oncological treatment;
— resection of symptomatic lesions of radiation necrosis after SRS/fSRS.

Radiotherapy

Stereotactic radiotherapy

Radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) can be performed with use of dedicated equipment (GammaKnife, CyberKnife, Edge) or conventional linear accelerators equipped with a high-definition multi-leaf collimator (HD-MLC). The total dose and fractionation depend on the location and size of metastatic lesions. In order to achieve local control, it is recommended to provide biologically effective dose higher than 100 Gy. The efficacy of SRS/fSRS in the treatment of small CNS melanoma metastases has been confirmed in many studies and is similar to surgical resection. Appropriate qualification of patients for treatment, which should be conducted by multidisciplinary teams, is very important.

Inclusion criteria for SRS/fSRS are:
— performance status 0–2 according to the World Health Organization (WHO) scale;
— single metastasis < 3 cm in diameter;
— a number of metastases > 1, when the total volume of the healthy brain irradiated with a dose of 12 Gy does not exceed 10 cm^3 (for single-fraction SRS);
— no progression outside the CNS or when potentially effective systemic treatment is available;
— indications for radiotherapy of postoperative bed [8, 21, 22];
— indications for possible repeated local irradiation when progression is confirmed;
— life expectancy > 6 months.

Radiosurgery, fractionated radiosurgery (stereotactic radiotherapy) was originally reserved for patients with fewer than 3 metastases; however, indications for this method have been recently extended [7]. According to them, the number of metastases is less important, and SRS is limited by the total volume of all lesions and brain volume, which receives a total dose of 12 Gy [23, 24]. It has been demonstrated that the volume of healthy brain tissue receiving a single dose of 12 Gy, which is greater than 10 cm^3, is associated with high risk of radiation necrosis. In this case, a reduction in the therapeutic dose or fSRS should be considered [25]. With proper qualification, the local efficacy of SRS/fSRS (no progression in the irradiated volume) is achieved in 90–95% of melanoma patients [26, 27]. A radiologically significant tumor response is observed in half of patients [26]. Local efficacy is closely related to the location of metastatic lesions and their size.

According to the ESMO recommendations, SRS/fSRS is the preferred method of adjuvant treatment after resection of melanoma metastases in the CNS [8].

Whole brain radiotherapy (WBRT)

Melanoma is considered to be radioresistant and sensitive only to higher doses per fraction. The fractionation regimens used for WBRT (5 × 4 Gy or 10 × 3 Gy) do not provide an adequate biological dose for long-term CNS disease control. Whole brain radiotherapy is associated with neurological toxicity. The deterioration in patient quality of life is mainly caused by the impairment of cognitive functions [28, 29]. Modern high-conformal radiotherapy techniques enable single isocenter SRS/fSRS for multiple brain metastases (hypothetically without a limited number of lesions if the criteria organs at risk are met, which also limits the use of WBRT) [30, 31].

In addition, the results of a phase III study published in 2019 indicate that WBRT should not be used as adjuvant treatment after resection of 1–3 melanoma metastases in the CNS [32].

Whole brain irradiation should only be reserved for the following patients:
— not eligible for surgery and SRS/fSRS;
— with rapid progression of metastases and inability or lack of efficacy of systemic treatment with proven value in the CNS;
— with leptomeningeal metastases (LMs) in good general condition.

Patients in poor general condition (WHO performance status 4) and with short life expectancy should be disqualified from any form of radiotherapy. The treatment of choice is best supportive care (BSC) (effective

anti-edematous and anti-convulsant treatment as well as alleviating symptoms that often accompany progression in the CNS).

Systemic treatment

Systemic treatment is the backbone therapy in patients with metastatic melanoma (including the CNS). Similar to molecularly targeted agents (BRAFi and MEKi), the use of immunotherapy (including anti-CTLA4, anti-PD1, and anti-PD-L1 drugs) significantly improves the prognosis of melanoma patients with CNS metastases. Currently, in the treatment of advanced disease, anti-PD-1 therapy combined with anti-LAG3 (nivolumab with relatlimab) is also used, although data on the use of this combination in patients with brain metastases are limited. Additionally, long-term remissions in immunotherapy responders are increasingly frequently observed, and drugs introduced into systemic therapy — both immunotherapy and molecularly targeted therapy — allowed for a significant extension of median OS [33]. The choice of appropriate systemic therapy should be determined by previously used treatment, presence of the V600 *BRAF* mutation, patient's condition, and clinical setting. In most patients, this therapy should be supplemented with local treatment. In the case of few and minor metastases in the CNS, only systemic treatment remains an option.

Molecularly targeted therapy

The efficacy of molecularly targeted drugs (BRAFi and MEKi) in patients with skin melanoma with CNS metastases has been shown in several prospective clinical trials. The first clinical trials conducted exclusively in this group of patients evaluated the efficacy of BRAFi in monotherapy. The largest study — involving 172 patients with asymptomatic CNS metastases — assessed the efficacy of dabrafenib (phase II BREAK-MB study). Patients included in this study were assigned into 2 groups depending on previous local treatment of CNS metastases (patients without prior local treatment *vs.* patients with progression after previous local treatment). The intracranial response rate was 39.2% and 30.8%, respectively. Median OS in both groups was over 8 months [2]. In a similar phase II clinical trial of vemurafenib in 146 patients with CNS metastatic skin melanoma, the intracranial response rate was 18%, regardless of previous local treatment. Median OS was approximately 9 months [34]. In the assessment of the response by an independent review committee (IRC), the intracranial response rates in both studies were very similar (approximately 18%). Both studies showed a high disease control rate (approximately 70–80%). In most patients, a reduction in CNS metastatic lesions was observed, but only in some patients, it met partial response criteria.

Symptomatic metastases in the CNS are associated with particularly poor prognosis (median OS — 3–4 months), and this is challenging. A clinical trial involving only patients with symptomatic metastases evaluated the use of vemurafenib in monotherapy [35]. This small study involved 24 patients who were ineligible for neurosurgical treatment after prior treatment of CNS metastases and required glucocorticoids for symptom control. The intracranial response rate was 16% and median OS was 5.3 months. During the treatment, pain relief, an improvement in patient performance status, and a decrease in the need for glucocorticoids were observed. Unfortunately, the treatment effect was short-term, and the disease progressed rapidly.

Combination of BRAFi with MEKi improved the results of targeted treatment. The phase II COMBI-MB study using dabrafenib with trametinib was the first prospective clinical trial evaluating the activity of this treatment in patients with CNS metastases [36]. The study included 125 patients with performance status 0–2 with or without prior local treatment for CNS metastases. Intracranial response rates were 56–59% regardless of previous local treatment and the presence of symptomatic metastases. Duration of response (DoR) was the longest in patients with asymptomatic CNS metastases. However, the median duration of response was much shorter than that observed in phase III clinical trials without the participation of patients with CNS metastases (approximately 6 months versus 12–14 months) [37–39]. However, there were no significant differences in treatment tolerance, with fever and gastrointestinal disorders being the most common. The efficacy of BRAFi/MEKi has also been confirmed in clinical practice, including in patients pretreated with these drugs. In a retrospective analysis of 24 patients with CNS metastatic *BRAF* mutant melanoma treated with encorafenib and binimetinib, the CNS objective response rate (ORR) was 33%, and the disease control rate (DCR) was 63%. In patients previously treated with BRAFi/MEKi, the ORR and DCR were 24% and 57%, respectively [40].

The results of these studies confirm the activity of the BRAFi/MEKi combination in patients with CNS metastases. The response to treatment is rapid, with most patients achieving tumor reduction. This effect significantly contributes to OS improvement in the group of patients with poor prognosis and quality of life, particularly in patients with symptomatic CNS metastases. Unfortunately, the above data also indicate a short-term therapeutic effect of this targeted therapy. Resistance develops faster than in patients without CNS metastases. Therefore, attempts to combine BRAFi/MEKi with other kinase inhibitors or immunotherapy to improve treatment outcomes are ongoing.

Table 3. Studies evaluating the efficacy of molecularly targeted therapy in the treatment of melanoma patients with metastases in the central nervous system (CNS)

Study	Patient characteristics	Number of patients	Median PFS [months]	Median OS [months]
Phase II study [34]	CNS metastases previously untreated	90	3.7	8.9
(NCT01378975)	CNS metastases after prior treatment	56	4.0	9.6
Vemurafenib				
Pilot study [35]	Previously treated, symptomatic CNS metastases	24	3.9	5.3
(NCT01253564)				
Vemurafenib				
Phase II study	CNS metastases without prior treatment of CNS metastases	89	~4[a]	~8[a]
BREAK-MB [2]				
(NCT01266967)	Progression after previous local treatment	83	~4[a]	~8[a]
Dabrafenib				
Phase II study	Asymptomatic CNS metastases without previous local treatment	76	5.6	10.8
COMBI-MB [36]	ECOG PS 0–1			
(NCT02039947)	Asymptomatic CNS metastases	16	7.2	24.3
Dabrafenib + trametinib	Prior local treatment			
	ECOG PS 0–1			
	Asymptomatic with/without prior local treatment	16	4.2	10.1
	ECOG PS 0–1			
	Symptomatic with/without prior local treatment	17	5.5	11.5
	ECOG PS 0–2			
GEM1802/EBRAIN-MEL [41, 42]	Asymptomatic CNS metastases	14	7.1	NA
(NCT03898908)	Symptomatic CNS metastases	15	9.3	18.4
Encorafenib and binimetinib in combination with radiotherapy				

[a]median applies to patients with the *BRAF* V600E mutation; ECOG — Eastern Cooperative Oncology Group; NA — data not available

The results of studies using BRAFi/MEKi in melanoma patients with CNS metastases are presented in Table 3 [2, 34–36, 41, 42].

Radiotherapy in combination with targeted treatment

High BRAFi/MEKi initial activity in melanoma patients with CNS metastases slightly changed the approach to using radiotherapy. Increasing use of SRS enables a high local control rate. Therefore, radiotherapy is often used only during BRAFi/MEKi treatment. Data on combining BRAFi drugs with concomitant radiotherapy are contradictory. On the one hand, there are potential benefits in terms of sensitization of melanoma cells to radiotherapy after BRAFi administration, which was described in *in vitro* studies [43]. On the other hand, the radiosensitizing effect of BRAFi can lead to increased side effects, which has been confirmed by several dozen case reports of significant skin toxicity with simultaneous use of irradiation (including WBRT) and BRAFi. It is worth mentioning, however, that these data refer only to older-generation BRAFi, currently replaced with newer molecules. New reports indicate that there is no need to interrupt treatment with newer-generation inhibitors. The data from the analysis of a small group of patients (GEM1802/EBRAINMEL study with encorafenib and binimetinib) indicate the possibility of improving treatment outcomes with new BRAFi/MEKs combined with radiotherapy [41, 42, 44, 45]. However, these findings were not reflected in the recommendations (as of 2023). There is no unequivocal evidence of an increased risk of neurotoxicity, hemorrhage, or radiation-related brain necrosis in the case of a combination of targeted treatment with radiotherapy [46–48]. In the case of conventional radiotherapy, the most common side effect is skin toxicity (more severe with vemurafenib) [49]. Currently, it is recommended to discontinue BRAFi/MEKi at least 3 days before the start of WBRT and to restart the drugs 3 days after completion of radiotherapy at the earliest. Withdrawal of molecularly targeted therapy is not justified when using SRS/fSRS [8].

Immunotherapy

Immunotherapy is the basic treatment option in melanoma patients with CNS metastases without V600 *BRAF* mutation. In patients with a mutation in the *BRAF* gene, the use of immunotherapy or BRAFi/MEKi treatment depends on the clinical situation.

In the open-label phase II study of ipilimumab (NCT00623766), the highest response rates were observed in asymptomatic patients not receiving glucocorticoids. Based on criteria for the immune-related response (IRR), median PFS in patients with CNS lesions was 1.9 months in the asymptomatic group *vs.* 1.2 months in the group requiring symptomatic treatment with glucocorticoids, and median OS was 7.0 *vs.* 3.7 months, respectively [50]. In the CheckMate 204 study (NCT02320058) with nivolumab and ipilimumab in glucocorticosteroids-naïve patients with at least one CNS lesion, the composite primary endpoint was the intracranial clinical benefit rate (CBR), consisting of objective responses and disease stabilization lasting more than 6 months. The CNS control rate was 55%, and the complete response rate reached 21%. Non-CNS responses were similar to those seen in the CNS, with a 6-month PFS rate of 67%. The results of the study confirm that, similar to the treatment of extracranial lesions, in patients with CNS metastases, it is possible to obtain a similar response to treatment for CNS lesions [51].

In 2019, updated results of the CheckMate 204 study in cohort A (patients with asymptomatic metastases in the CNS, e.g. without neurological symptoms and not taking glucocorticoids) and cohort B (patients with neurological symptoms regardless of glucocorticoid use) were presented. Patients in both groups received nivolumab at a dose of 1 mg/kg body weight (bw) and ipilimumab at a dose of 3 mg/kg bw every 3 weeks (4 administrations), and then only nivolumab at a dose of 3 mg/kg bw every 2 weeks until disease progression or treatment toxicity. In cohort A, after a follow-up of 20.6 months, the CBR was 58.4%, and in cohort B, after a follow-up of 5.2 months, it was 22.2%. Grade 3 and 4 treatment-related adverse events were observed in 54% of patients in cohort A and 56% of patients in cohort B. Grade 3 and 4 treatment-related neurologic adverse events occurred in 7% and 17% of patients, respectively [52, 53]. Similarly, the Australian ABC study (NCT02374242), which compared nivolumab versus nivolumab with ipilimumab in 79 melanoma patients with CNS metastases, demonstrated the efficacy of immunotherapy (including the advantage of doublet therapy in melanoma patients with asymptomatic CNS metastases). In the ABC study, patients were assigned to 3 cohorts: A (asymptomatic patients not treated locally due to CNS metastases receiving ipilimumab with nivolumab; n = 36), B (asymptomatic patients not treated locally due to CNS metastases and receiving nivolumab; n = 27) and C (patients after failure of local treatment of CNS metastases, or symptomatic patients with CNS metastases, and patients with LM and receiving nivolumab; n = 16). Complete responses to treatment were observed in 17% of patients in cohort A and 12% of patients in cohort B (cohort C — no response) [54, 55].

In the CheckMate 204 study and ABC study, grade 3 and 4 treatment-related adverse events occurred in 52% and 54% of patients receiving doublet therapy, respectively.

In asymptomatic patients, the presented clinical trials demonstrated the efficacy and good tolerance of immunotherapy. With ipilimumab, the response rate was as high as 16%, and with nivolumab and pembrolizumab it was approximately 20%. In studies on the combination of anti-PD-1 and anti-CTLA-4 agents in the group of asymptomatic patients, further significant improvement in treatment results was obtained. In patients with symptomatic metastases, the intracranial clinical response rate was also significant and amounted to 16.7%. With the availability of anti-PD-1 and anti-CTLA-4 combination therapy (nivolumab with ipilimumab — regardless of *BRAF* gene mutation status) and anti-BRAF and anti-MEK therapy in patients with mutation in the *BRAF* gene and good performance status, it is the treatment of choice, especially in the case of asymptomatic metastases in the brain, with the option of postponing local treatment until disease progression in patients receiving combined therapy.

Overall, the safety profile of immunotherapy in the aforementioned studies was consistent with that for patients without brain metastases. Moreover, intracranial and extracranial responses were largely consistent, which was confirmed by the results of a meta-analysis published by Rulli et al. in 2019 [56].

The choice of systemic therapy after diagnosis of CNS metastases remains an important issue.

The authors of an analysis published in 2023 retrospectively assessed the results of treatment in patients after first-line therapy due to generalized melanoma without CNS metastases (n = 1704), with and without the *BRAF* mutation. In patients with *BRAF* mutation-positive melanoma undergoing first-line anti-PD1 and anti-CTLA4 immunotherapy, brain metastases occurred less frequently and later as compared to BRAFi and MEKi therapy. In addition, the use of doublet immunotherapy was associated with longer OS. Interestingly, no differences in terms of OS were found between dual immunotherapy and anti-PD-1 monotherapy in melanoma patients without the *BRAF* mutations [57].

Derks et al. [58] published 2023 an analysis of melanoma patients with CNS metastases treated in daily

Table 4. Studies evaluating the efficacy of immunotherapy in the treatment of melanoma patients with metastases in the central nervous system (CNS)

Treatment	Patients	Patient characteristics	IC DCR	IC ORR	IC DOR [months]	mPFS [months]	mOS [months]
Ipilimumab	51 (A)	Asymptomatic	24%	16%	–	1.4	7.0
CA184-042 [50]	21 (B)	Symptomatic	10%	5%		1.2	3.7
Ipilimumab + fotemustine: NIBIT-M1 [59]	20	Asymptomatic	50%	40%	30.3	4.5	12.7
Pembrolizumab: (NCT02085070) [60, 61]	23	Untreated or progressive brain metastases	–	26%	–	2	17
Nivolumab: ABC; CA209-170 [54] (NCT02374242)	27 (B)	Asymptomatic, no local treatment (B)	20%	20%	NR	2.5	18.5
	16 (C)	previously treated or symptomatic (C)	19%	6%	NR	2.3	5.1
Nivolumab + ipilimumab: ABC; CA209-170	36 (A)	Asymptomatic, no local treatment (A)	57%	46%	NR	NR	NR
Nivolumab + ipilimumab: CheckMate 204 [52, 53] (NCT02320058)	75	Asymptomatic, previously treated, ≤ 3 metastases	60%	55%	NR	NR	–

IC DCR — intracranial diseases controls rate; IC DOR — intracranial duration of response; IC ORR — intracranial objective response rate; NR — not reached; OS — overall survival; PFS — progression-free survival

clinical practice in Rotterdam from 2005 to 2021, comparing the period before and after the introduction of new treatment methods (cut-off point 2015). In total, 430 patients were analyzed, and OS was assessed before and after 2015 when checkpoint inhibitors and molecularly targeted therapy began to be used much more frequently. The analysis included 152 melanoma patients with CNS metastases before 2015 and 278 treated after 2015. Median OS in patients treated after 2015 was significantly longer compared to patients treated before 2015 (6.9 *vs.* 4.4 months, hazard ratio 0.67, $p < 0.001$). Median OS was shorter in patients who received systemic treatment before the diagnosis of CNS metastases. The use of immunotherapy immediately after the diagnosis of CNS metastases was associated with an increase in median OS from 4.2 months to 21.5 months ($p < 0.001$). BRAF and MEK inhibitors can cause a rapid response to treatment and have been frequently administered (> 70%) in patients with symptomatic metastases and poor performance status [58].

Studies have also been conducted to evaluate sequential and combination therapy with BRAF and MEK inhibitors and immunotherapy in melanoma patients with CNS metastases. The combined use of atezolizumab plus vemurafenib and cobimetinib resulted in an intracranial response rate of 42% and median OS of 13.7 months. In some situations, the above regimen may be an option in subsequent treatment lines, but currently, the combination of BRAF and MEK inhibitors with immunotherapy is not a standard of care.

The results of studies using immunotherapy in melanoma patients with CNS metastases are summarized in Table 4 [50, 52–54, 59–61] while the results of studies evaluating the efficacy of molecularly targeted therapy combined with immunotherapy are presented in Table 5 [62–65].

Combining radiotherapy with immunotherapy

There are more and more reports related to the beneficial effect of combining radiotherapy with immunotherapy. The studies published so far have shown a significant increase in the percentage of abscopal effect phenomenon (response of untreated lesions to local treatment of another lesion) after adding radiotherapy to immunotherapy [66, 67]. The effect is explained by local stimulation of the immune system and intensification of antigenic effect, where dendritic cells probably play an important role. Currently, many clinical trials are conducted in which radiotherapy and immunotherapy are combined. There are no contraindications to combining radiotherapy with immunotherapy, and this decision should be made at a multidisciplinary meeting individually for each patient [8]. Attention should be paid to the prophylactic anti-edematous treatment administered during radiotherapy in the form of high doses of glucocorticosteroids, which may reduce immunotherapy efficacy. According to the current recommendations, indications for the use of glucocorticosteroids as part of anti-edematous treatment during SRS/fSRS are significantly limited.

Table 5. Studies evaluating the efficacy of molecularly targeted therapy combined with immunotherapy in melanoma patients with the *BRAF* mutation and metastases in the central nervous system (CNS)

Study	Study phase	Treatment	Number of patients	IC ORR % (CR + PR)	mPFS [month]	mOS [month]
TRIDENT [62] Patients with anti-PD1 resistance (n = 17) or previous or current brain metastases, including active metastases, asymptomatic metastases, or mild symptoms/requiring corticosteroids (n = 10)	II	Nivolumab + + dabrafenib + + trametinib	10	4/7 patients (57%)	8.0	NR
IMSpire 150 [63, 64] Exploratory analysis	III	Vemurafenib + + cobimetinib + + atezolizumab *versus* vemurafenib + + cobimetinib	244 *versus* 247	Cumulative incidence of brain metastasis as the first site of progression: after 12 months: 16% *vs.* 19% after 24 months: 24% *vs.* 26% after 36 months: 25% *vs.* 28% after 48 months: 28% *vs.* 29% Stratified HR = 0.91; 95% CI 0.64–1.29		
TRICOTEL [65] (Cohort 1: *BRAF* V600 positive melanoma patients with brain metastases; n = 15; Cohort 2: *BRAF* V600 negative melanoma patients with brain metastases)	II	Atezolizumab + + vemurafenib + + cobimetinib	65	42 IRC-assessed (51 investigator-assessed)	5.3 IRC-assessed (5.8 investigator-assessed)	13.7

CI — confidence interval; CR — complete response; HR — hazard ratio; IC ORR — intracranial objective response rate; ICR — independent review committee; NR — not reached; OS — overall survival; PFS — progression-free survival; PR — partial response

The combination of immunotherapy or molecularly targeted therapy with SRS/fSRS seems to be generally well tolerated, as demonstrated by studies and analyses conducted so far. In 2016, the results of a retrospective analysis conducted in a subgroup of patients participating in two prospective studies with nivolumab due to unresectable or metastatic disease were published [68]. Twenty-six patients treated for melanoma and undergoing SRS/fSRS due to CNS metastases were analyzed, including patients with CNS metastases diagnosed and treated with SRS within 6 months of nivolumab treatment (before, after, or during immunotherapy). A total of 73 lesions in the CNS were identified in this group of patients. The primary endpoint was treatment tolerance, while the secondary endpoints included control of CNS disease, lesions outside the CNS, and OS. Most metastatic patients were treated with SRS, and only 12 CNS lesions underwent fSRS. Grade 2 headache was observed in one patient, which resolved after using glucocorticoids. No other treatment-related neurological complications were observed. In 8 CNS lesions (11%), treatment failure was observed in the form of an increase in lesion volume of at least 20%. Local control rates at 6 and 12 months were 91% and 85%, respectively. Median OS was 12.0 months from initiation of nivolumab treatment and 11.8 months from SRS/ fSRS.

In 2017, a systematic review was published to assess the tolerance of the combination of immunotherapy or targeted therapy with SRS/fSRS. The review included 6 retrospective studies and 2 case reports on patients treated with SRS/fSRS and ipilimumab. Based on this analysis, it can be concluded that the combination of ipilimumab and SRS/fSRS for intracranial lesions is a safe treatment option [69].

New methods of systemic treatment in melanoma patients with CNS metastases

Due to often short-term or insufficient response to immunotherapy or molecularly targeted therapy in melanoma patients with CNS metastases, attempts are currently being made to combine BRAF/MEK inhibitors with other kinase inhibitors or immunotherapy to improve the outcomes. An example is the TRIDeNT study with the use of nivolumab in combination with dabrafenib and/or trametinib, involving melanoma patients with CNS and leptomeningeal metastases (NCT02910700) [62]. Another interesting trial is

the NCT05704933 study with the perioperative use of nivolumab in combination with ipilimumab or relatlimab in patients with resectable melanoma metastases in the CNS [70]. Strategies based on systemic therapy combined with radiotherapy are also being evaluated. An example is the phase II BEPCOME-MB study, in which binimetinib with encorafenib and pembrolizumab are used together with SRS/fSRS in patients with *BRAF* mutation-positive melanoma and CNS metastases (NCT04074096) [71].

Monitoring of patients after local treatment due to CNS metastases and management in case of progression

The melanoma brain metastases occurrence is associated with an increased risk of new brain metastases. This justifies the regular brain MRI in all patients treated due to melanoma with CNS dissemination [7]. In approximately 50% of patients, new metastatic lesions or progression of previously treated metastases (recurrence in the postoperative bed, progression after SRS/fSRS/WBRT) will be detected [72]. The first MRI is recommended within a month after neurosurgery or SRS, and every 2–3 months afterwards. The results of imaging tests should be interpreted with caution, especially in patients receiving immunotherapy due to the risk of pseudoprogression and/or posttreatment lesions that may be difficult to distinguish from real disease progression. Despite the introduction of modern neuroimaging techniques, it is difficult to determine the nature of the detected changes (progression of an active neoplastic process or radiation necrosis). In doubtful situations, resection should be the treatment of choice, because — apart from oncological indications — removal of necrotic tissues reduces brain edema. In order to differentiate between radiation necrosis and disease recurrence, magnetic resonance spectroscopy (MRS) may be considered [73]. It is helpful to use structured assessment methods, such as the RANO (Response Assessment in Neuro-Oncology) criteria [74].

In the case of CNS progression, it is usually possible to use one of the local salvage treatments (resection, SRS/fSRS, WBRT) after discussing the patient's case at a multidisciplinary meeting [75–78]. There are possible two different scenarios. If progression is found outside the irradiated volume, it is usually possible to use SRS/fSRS or WBRT. In the case of progression within the irradiated volume, emergency surgical treatment remains the method of choice, with maintaining the previously described qualification criteria for neurosurgical treatment.

Leptomeningeal metastases

The prognosis of patients with leptomeningeal metastases is poor and survival usually does not exceed a few weeks. Data on the efficacy of modern systemic therapies in patients with meningeal involvement are limited, and evidence-based standards of management are missing. The results of recently published retrospective analyzes indicate that molecularly targeted therapy and immunotherapy may improve the prognosis in these patients [79, 80]. A phase I clinical trial (NCT03025256) is currently conducted with the use of systemic and intrathecal nivolumab in patients with leptomeningeal disease.

Data on systemic use of interleukin-2 (IL-2) are encouraging — 1-, 2-, and 5-year survival rates in the group of 43 patients were 36%, 26%, and 13%, respectively. However, due to increased toxicity, the use of IL-2 is not a standard procedure [81].

Radiotherapy in the form of WBRT involving the meninges up to level C2 is a palliative treatment and should be used only in a selected group of patients (good general condition, active systemic treatment).

Summary

The basic and applicable rule in the management of melanoma metastases in the CNS should be a multidisciplinary approach involving, at least, a neurosurgeon, radiation oncologist and clinical oncologist experienced in the treatment of melanoma patients with CNS metastases. There are no clear risk factors for melanoma brain metastases. The detection of CNS metastases is associated with poor prognosis; they are the cause of death in 20–50% of patients, and symptomatic tumors are the immediate cause of death in about 90% of patients. Historical data indicated a median OS of 5–7 months after the diagnosis of CNS metastasis. Currently, more and more CNS metastases are diagnosed at the asymptomatic stage using routine brain imaging during the follow-up or qualification for systemic treatment. Treatment of melanoma with CNS metastases includes, depending on the clinical situation, local and/or systemic therapy and symptomatic treatment. In local treatment, advanced techniques of stereotactic radiotherapy are the most valuable. During the last 10 years, 11 new drugs have been registered in Europe for the treatment of patients with advanced melanoma. Due to the introduction of modern systemic therapies, median OS is now about 2 years, based on data from clinical trials. Anti-PD1 and anti-CTLA-4 dual therapy (nivolumab with ipilimumab), when available, can be the choice in patients with CNS metastasis up to 3 cm in diameter and with good performance status. BRAF

inhibitors and MEKi can be the upfront treatment in patients with *BRAF* mutation and asymptomatic metastases.

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