VIA MEDICA

REVIEW ARTICLE

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Efficacy of targeted therapies in the treatment of patients with melanoma harboring *BRAF V600* mutation with central nervous system metastases

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Translation: Dariusz Stencel, MD PhD, MBA
DOI: 10.5603/ocp.102692
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ISSN 2450–1654
e-ISSN 2450–6478

ABSTRACT

Brain metastases develop in almost half of patients with advanced melanoma, and in about 20% of patients, they are the first location of disseminated disease. In the past, the median survival of these patients was about four months, and one-year survival rate was only 10–20%. The implementation of new treatments, including stereotactic radiosurgery, immunotherapy and targeted therapy has significantly improved the prognosis. Approximately 50–60% of melanomas harbor mutations in the *BRAF* gene, so the use of BRAF/MEK inhibitors, which allow for a high rate of intracranial responses, is one of the management options. Many melanoma patients with brain metastases require various therapeutic methods, including local and systemic therapy and their selection and sequence depend on many clinical parameters. Diagnostic and therapeutic management in this group of patients is currently a great challenge. The aim of this publication is to summarize the effectiveness of targeted therapies in the treatment of melanoma patients with a mutation in the *BRAF* gene and central nervous system metastases.

Keywords: melanoma, *BRAF* mutation, targeted therapy, brain metastases

Oncol Clin Pract 2024; 20, suppl. A: A3–A9

Introduction

Incidence of melanoma is increasing worldwide. It is the third most common malignant tumor, after breast and lung cancer, in terms of the frequency of brain metastases. The central nervous system (CNS) is a common site of disease recurrence and progression in melanoma patients. The presence of brain metastases significantly worsens the prognosis. CNS lesions develop in almost half of patients with advanced melanoma, with 30–40% of patients having them already at diagnosis of disseminated disease, and 80% of patients with disseminated melanoma have CNS metastases at the time of death. In almost 20% of melanoma patients, CNS is the first location of metastases. In 3% of melanoma patients with brain metastases, the primary site cannot be determined.

CNS metastases are often multifocal and initially asymptomatic, with a tendency to bleed. In the past, the prognosis in melanoma patients with brain metastases was very poor, the median survival was four months and only 10–20% of patients had a chance to survive a year. The introduction of new methods of local and systemic treatment has improved the prognosis and allowed for survival prolongation. Due to characteristic for melanoma spreading of disease to CNS, the last update, 8th edition of the American Joint Committee on Cancer (AJCC) staging classification distinguishes brain metastases as a separate stage IV category (M1d) [1]. Predictors of CNS involvement in melanoma patients have not been established yet.

The risk of brain metastases increases with melanoma stage. Factors associated with a higher risk include

Translation and republished by permission from: Dudzisz-Śledź M, Rutkowski P. Skuteczność terapii ukierunkowanych molekularnie w leczeniu chorych na czerniaka z mutacją *V600* w genie *BRAF* z przerzutami do ośrodkowego układu nerwowego. Onkol Prakt Klin Edu 2023; 9(supl. E): E3–E10.

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the location of the primary lesion in the head and neck, increased lactate dehydrogenase (LDH) level, presence of ulceration in the primary lesion, and harboring of mutations in the *BRAF*, *NRAS*, and *PTEN* genes [2]. Brain lesions may be asymptomatic, especially at the beginning. Their growth is usually accompanied by symptoms resulting from pressure and edema, including speech impediments, swallowing disorders, paresis and paralysis, epilepsy, headaches and dizziness, nausea, vomiting and bradycardia. These symptoms adversely affect the patient's general condition. Awareness of the high risk of melanoma metastases to the brain and related diagnostics consisting of routine brain imaging as part of the follow-up and during qualification for systemic treatment, allow for detection of CNS metastases at the asymptomatic stage, when both the patient's condition and systemic treatment outcomes are better.

Metastasizing to the brain is a major challenge in the management of melanoma. Patients' care should be provided by multidisciplinary team (MDT) with the participation of specialists experienced in the diagnosis and treatment of this disease, including a neurosurgeon, radiotherapist and clinical oncologist, because the therapy may include both local (radiotherapy, neurosurgery) and systemic treatment as well as supportive (symptomatic) care [3]. The choice and sequencing of individual treatment methods depends on many clinical factors. In the systemic treatment of melanoma, also with metastases to the CNS, immune checkpoint inhibitors (ICIs) (anti-PD-1, anti-LAG3, anti-CTL-A4) and BRAF and MEK inhibitors are currently used. In approximately 40–60% of melanomas, mutations are found in the *BRAF* gene, and in this group of patients, treatment with targeted therapies, BRAF and MEK inhibitors, is justified.

A mutation in the gene encoding the BRAF protein leads to constitutive activation of MAP kinase signaling pathway. In 80–90% of these cases, the activating mutation consists of replacing valine with glutamic acid at amino acid 600 (V600E). The presence of mutations in the *BRAF* gene is associated with a worse prognosis and distinct clinical characteristics of melanoma. In a case series including 197 melanoma patients, Long et al. [5, 6] demonstrated that *BRAF* mutations were associated with high-risk melanoma features, including location in the trunk, disease onset at a younger age, lack of chronic skin damage, and shorter survival [4]. *BRAF*-mutated melanomas more frequently metastasize to the CNS. In patients with *BRAF* mutations, the choice of systemic treatment depends, among others, on clinical characteristics, including different factors, such as the curse of previous treatment, location and clinical characteristics of extracranial lesions, patient's performance status (PS), comorbidities and concomitant drugs.

A review and meta-analysis published in 2019 showed that dual immunotherapy and doublet targeted therapy allow to achieve similar intracranial response rates, while dual immunotherapy allows for longer progression-free survival (PFS) and overall survival (OS) compared to single-drug immunotherapy and targeted therapy [7]. According to current guidelines (NCCN, ESMO), in patients with *BRAF*-mutated melanoma with brain metastases, especially asymptomatic and less than 3 cm in size, not requiring corticosteroids, dual immunotherapy is recommended, which shows the greatest activity in CNS lesions, unless contraindicated. Its efficacy is higher in *BRAF*-positive melanomas compared to *BRAF*-negative ones.

However, depending on the clinical situation, the use of BRAF and MEK inhibitors in the first line treatment should be also considered. BRAF and MEK inhibitors are more often used as treatment of choice in symptomatic brain metastases or in the case of progression after immunotherapy. Therapeutic decisions should be individualized, based on clinical features such as LDH level, involvement of other organs, tumor mass, patient's performance status, course of the disease, comorbidities, size and location of CNS lesions, leptomeningeal carcinomatosis and its treatment, as well as patient preferences and treatment goals (short-term versus long-term benefits). All decisions should be made within multidisciplinary team [8–10].

The use of targeted therapies in the treatment of patients with *BRAF V600*-mutated melanoma with central nervous system metastases

Systemic treatment is well established as a backbone therapy in patients with *BRAF*-mutated melanoma with CNS metastases, which significantly improves prognosis. The choice of treatment regimen depends on many factors, including the presence of the V600 mutation in the *BRAF* gene, patient's performance status, clinical characteristics of intra- and extracranial disease, previous melanoma treatment, comorbidities and concomitant drugs, and patient's preferences. Systemic treatment is usually supplemented with appropriate local treatment.

The efficacy of molecularly targeted drugs (BRAF and MEK inhibitors) in melanoma patients with brain metastases has been demonstrated in prospective clinical trials. The first of these studies evaluated the efficacy of BRAF inhibitors in monotherapy. The largest of them was the phase II BREAK-MB study (n = 172) with dabrafenib in melanoma patients with asymptomatic CNS metastases. The intracranial response rate (IRR) was 39.2% in patients without previous local treatment for CNS metastases and 30.8% in patients with progression after prior local treatment. The median OS in both groups was more than 8 months [11]. In a phase II study

with vemurafenib (n = 146), the IRR was 18% regardless of the previous local treatment, and the median OS was about 9 months [12]. In independent review the IRR in both studies was about 18%, and the disease control rate (DCR) was about 70–80%.

The efficacy of vemurafenib in monotherapy was also assessed in a small study in patients with symptomatic brain metastases not eligible for neurosurgery and requiring corticosteroids (n = 24) [13]. The IRR was 16%, and the median OS was 5.3 months. Whilst performance status and pain improved, with decreased need for corticosteroids, disease progression in the CNS was relatively rapid, despite the initial improvement. The combination of BRAF inhibitors with MEK inhibitors was associated with targeted therapy outcomes, also in melanoma patients with brain metastases.

In the prospective phase II COMBI-MB clinical trial with dabrafenib and trametinib (n = 125) in patients with good performance status (ECOG PS 0–2) and CNS metastases, previously treated and not treated locally for CNS lesions, the IRR was 56–59%, regardless of previous local treatment and presence of clinical signs and symptoms [14]. In asymptomatic patients, the treatment response maintained longer than in symptomatic patients. The duration of response was approximately six months (median) and was significantly shorter than in phase III studies in patients without CNS metastases (12–14 months) [14–16]. The most frequently observed adverse events were fever and gastrointestinal disorders, similarly to other studies with dabrafenib and trametinib.

In an analysis of patients after first line treatment for metastatic melanoma without CNS metastases (n = 1704), published in 2023, the authors retrospectively analyzed the treatment outcomes depending on *BRAF* mutation status. In melanoma patients with *BRAF* mutation treated with anti-PD-1 and anti-CTLA4 immunotherapy in the first line, brain metastases occurred less frequently and later than in patients receiving anti-BRAF and anti-MEK therapy. In addition, the use of dual immunotherapy was associated with a longer OS. Interestingly, no differences in OS were shown between dual immunotherapy and anti-PD-1 monotherapy in melanoma patients without *BRAF* mutations [17].

In 2023 Derks et al. [18] published real-world evidence (RWE) from melanoma patients with brain metastases treated at Rotterdam center from 2005 to 2021 (n = 430), comparing the outcomes achieved before and after the introduction of new therapies (cutoff year 2015). Overall survival was assessed before and after 2015, when ICIs and targeted therapies were used much more frequently. The analysis included 152 melanoma patients with CNS metastases treated before 2015 and 278 patients treated after 2015. The median OS in patients treated after 2015 was significantly longer compared to patients treated before 2015 (6.9 *vs*. 4.4 months, HR 0.67, $p < 0.001$). Median OS was shorter in patients who received systemic therapy before detection of brain metastases. Immunotherapy administered immediately after diagnosis of CNS metastases was associated with prolongation of median OS from 4.2 months to 21.5 months ($p < 0.001$) [18]. As BRAF and MEK inhibitors can induce a rapid treatment response, these drugs were frequently used (> 70%) in patients with symptomatic melanoma brain metastases (MBM) and poor performance status.

BRAF and MEK inhibitors allow for a response in most patients, usually after a short period of use, which may improve the quality of life, especially in symptomatic patients. Unfortunately, the response to targeted drugs is relatively short-term and resistance develops over time.

The results of the studies conducted so far, that confirmed the activity of BRAF and MEK inhibitors in melanoma patients with brain metastases, are summarized in Table 1.

The efficacy of BRAF and MEK inhibitors has also been confirmed in clinical practice, including patients previously treated with these drugs. In a retrospective analysis of 24 patients with *BRAF*-mutated melanoma and CNS metastases treated with encorafenib and binimetinib, the objective response rate (ORR) in the CNS was 33%, disease control rate (DCR) was 63%, as compared to 24% and 57%, respectively, in patients previously treated with BRAF and MEK inhibitors. Only 3 of the 24 patients had not been previously treated with BRAF and MEK inhibitors, and they achieved a partial treatment response in CNS, while two of them achieved a complete CNS response. Among 21 patients, who had previously been treated with BRAF and MEK inhibitors, 11 patients discontinued previous therapy due to poor tolerance and 10 due to disease progression. Encorafenib and binimetinib were well tolerated. Adverse events were observed in 16 patients (67%), the most common of which were fatigue (17%) and myalgia (13%), as well as retinal detachment (8%), arthritis (8%), and nausea (8%). Adverse events were grade 1 or 2, except for two patients who experienced grade 3 myalgia. Pyrexia was observed in one patient [23].

The results of treatment of melanoma patients with brain metastases have significantly improved thanks to the use of new systemic therapies. In many cases systemic therapy is combined with local treatment, which may include both neurosurgery and radiotherapy. In selected patients local treatment includes both of these modalities. Currently, radiotherapy is often used during treatment with BRAF and MEK inhibitors. The combined use of radiotherapy and targeted therapy allows for sensitization of melanoma cells to radiation through the use of BRAF inhibitors, but at the same time may increase the risk and severity of potential adverse effects,

Table 1. Clinical trials evaluating the efficacy of BRAF and MEK inhibitors in the treatment of patients with *BRAF*--mutated melanoma with brain metastases

Study	Type of analysis, phase	Treatment	n	IC ORR % (CR + PR)	mPFS [months]	mOS [months]
Dummer R. [13]	2.	vemurafenib	24	16	3.9	5.3
Falchook GS [19]	1.	dabrafenib	10	NA	4.2	NA
Arance AM [20]	3.	vemurafenib	66	18	NA	NA
BREAK-MB [11] (dabrafenib) (Cohort A: no prior local treatment; Cohort B: progression after prior local treatment)	2.	Cohort A *BRAF V600*E	74	39.2	3.7	7.6
		Cohort A *BRAF V600*K	15	6.7	1.9	3.8
		Cohort B *BRAF V600*E	65	30.8	3.8	7.2
		Cohort B *BRAF V600*K	18	22.2	3.7	5.1
McArthur GA [12] (Vemurafenib (Cohort 1: no prior treatment for brain metastases; Cohort 2: patients previously treated for brain metastases)	2.	Cohort 1	90	18	3.7	8.9
		Cohort 2	56	18	4.0	9.6
Geukes Foppen MH [21]	Retrospective analysis	dabrafenib + trametinib	30	NA	5.8	11.2
Drago JZ [22]	Retrospective analysis	dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib, vemurafenib + trametinib	65	NA	5.3	9.5
Holbrook K [23]	Retrospective analysis	encorafenib + binimetinib	24	33	NA	NA
COMBI-MB [14] (dabrafenib + trametinib) (Cohort A: asymptomatic untreated brain metastases; Cohort B: asymptomatic previously treated brain metastases; Cohort C: asymptomatic brain metastases of *BRAF V600*K/D/R mutation-positive melanoma; Cohort D: symptomatic brain metastases)	2.	Cohort A	76	58	5.6	10.8
		Cohort B	16	56	7.2	24.3
		Cohort C	16	44	4.2	10.1
		Cohort D	17	59	5.5	11.5
GEM1802/EBRAIN-MEL (encorafenib and binimetinib in combination with radiotherapy) [24, 25] (Cohort 1: asymptomatic brain metastases; Cohort 2: symptomatic brain metastases)	2.	Cohort 1	14	64	7.1	NA
		Cohort 2	15	73	9.3	18.4

IC ORR — intracranial objective response rate; CR — complete response; PR — partial response; PFS — progression-free survival; OS — overall survival; NA — data not available; n — number of patients

e.g., skin toxicity during whole brain radiation therapy (WBRT). It is recommended to withhold BRAFi/MEKi therapy for at least three days before starting WBRT and to resume no earlier than three days after completing radiotherapy.

Currently, stereotactic radiosurgery (SRS) is increasingly used, which allows for a high local control rate. In the case of SRS, systemic therapy is not required to be withhold [8, 24–27]. Concomitant use of BRAF and MEK inhibitors with concurrent radiotherapy is well tolerated and safe, as proven in the phase II GEM1802/ /EBRAIN-MEL clinical trial (NCT03898908), in which encorafenib and binimetinib were used in combination with radiotherapy [24, 25, 28]. The results of this study suggest that outcomes of treatment with novel BRAF and MEK inhibitors combined with radiotherapy may be improved without increased toxicity related to addition of radiotherapy. GEM1802 was a prospective phase II clinical trial in which melanoma patients with CNS metastases received encorafenib (450 mg daily) and binimetinib (45 mg BID) for 56 days, followed by CNS radiotherapy (local or WBRT) and continued encorafenib plus binimetinib until disease progression. The study included 27 patients without signs and symptoms of CNS metastases and 15 symptomatic patients.

The primary endpoint was ICR after 56 days of systemic therapy, i.e., before the start of radiotherapy. Only patients with disease stabilization or partial response to systemic treatment were qualified for radiotherapy. During the median follow-up of 12.3 months, disease progression was not observed in patients receiving systemic treatment. ICR after 56 days of therapy was 66.7% in asymptomatic patients and 73.3% in symptomatic patients. Radiotherapy was administered to 30 patients, including local irradiation in 15 patients and WBRT in 15 patients. In symptomatic patients who did not achieve a complete intracranial response and received radiotherapy, the duration of response was longer compared to patients who did not receive radiotherapy (8.6 months *vs*. 5.6 months). No significant increase in systemic toxicity was observed after radiotherapy use [28].

Unfortunately, the treatment response in melanoma patients with CNS metastases is often unsatisfactory or short-term. Further clinical trials are being conducted to evaluate potential systemic treatments with the aim of improving these outcomes. Among others, trials are currently underway to combine BRAF and MEK inhibitors with other kinase inhibitors or immunotherapy or local treatments. Published results of studies on combination therapies are summarized in Table 2.

Table 2. Clinical trials evaluating the efficacy of targeted therapy combined with immunotherapy in the treatment of patients with BRAF-mutated melanoma with brain metastases.

Study	Phase	Treatment	n	IC ORR % (CR + PR)	mPFS (months)	mOS (months)
TRIDeNT [31] Patients with anti-PD1 resistance (n = 17) or with previous or current brain metastases, including active, asymptomatic or mildly symptomatic/requiring steroids metastases (n = 10)	2.	nivolumab + dabrafenib + trametinib	10	4/7 patients (57%)	8.0	NA
IMSpire 150 [29, 30] Exploratory analysis	3.	vemurafenib + cobimetinib + atezolizumab *vs.* vemurafenib + cobimetinib	244 *vs.* 247	Cumulative incidence of brain metastases as first site of progression: at 12 months: 16% *vs.* 19% at 24 months: 24% *vs.* 26% at 36 months: 25% *vs.* 28% at 48 months: 28% *vs.* 29% Stratified HR: 0.91; 95%: 0.64–1.29)		
TRICOTEL [32] (Cohort 1: *BRAF V600*--negative melanoma patients with brain metastases; n = 15; Cohort 2: *BRAF V600*-mutated melanoma patients with brain metastases)	2.	atezolizumab + vemurafenib + cobimetinib	65	42 in IRC assessment (51 in investigator assessment)	5,3 in the IRC assessment (5.8 in investigator assessment)	13.7

IC ORR — intracranial objective response rate; CR — complete response; PR — partial response; PFS — progression-free survival; OS — overall survival; NA — data not available; ICR — independent review committee; HR — hazard ratio; n — number of patients

Table 3. Currently conducted clinical trials with targeted therapies in melanoma patients with central nervous system metastases

NCT number	Title and phase	Endpoints
NCT04074096 [33]	Randomized phase II clinical trial of adding upfront stereotactic radiosurgery to binimetinib, encorafenib, and pembrolizumab versus binimetinib, encorafenib, and pembrolizumab in patients with *BRAF V600*-mutant melanoma with brain metastases	CNS progression-free survival
NCT04511013 [34]	Phase II clinical trial comparing encorafenib plus binimetinib plus nivolumab versus ipilimumab plus nivolumab in patients with *BRAF V600*-mutated melanoma with brain metastases	Progression-free survival based on RECIST 1.1 criteria
NCT03332589 [35]	Phase 1 clinical trial of E6201 (MEK inhibitor) plus dabrafenib in the treatment of patients with BRAF-mutant melanoma with central nervous system metastases	Intracranial response rate based on RANO-BM criteria

The results of the IMSpire 150 study, in which patients receiving atezolizumab and vemurafenib in combination with cobimetinib achieved ICR of 42% and median OS of 13.7 months [29, 30] show that in selected cases combination of targeted therapy with immunotherapy may be an option; however, it is not a current standard of care. Selected ongoing clinical trials are presented in Table 3.

Conclusions

Melanoma is a malignant tumor often associated with brain metastases, which significantly worsens the prognosis. Treatment should be carried out in a multidisciplinary team, with the participation of experienced specialists. Whilst systemic therapy is backbone therapy, neurosurgery and radiotherapy are also used. Treatment should be individualized and based on clinical characteristics of disease, patient general condition, comorbidities and patient preferences. There are no results of head-to-head studies comparing the available systemic therapies, also in combination with local treatment.

Currently, dual immunotherapy is recommended for asymptomatic patients with CNS metastases smaller than 3 cm, regardless of *BRAF* mutation status. In approximately 40–50% of melanomas, the *V600E* mutation in the *BRAF* gene is found. In patients with melanoma with *BRAF* gene mutation, BRAF and MEK inhibitors should be considered, as their efficacy in terms of intracranial response rate is similar to dual immunotherapy.

The decision regarding systemic treatment should take into account the patient's preferences. Patients should also be qualified for local treatment. BRAF and MEK inhibitors may also be used in subsequent treatment lines in patients who have previously received these drugs. Whilst prognosis in patients treated with modern therapies has improved significantly, many patients still experience disease progression despite their use. Clinical trial participation, if available, remains a valuable option in melanoma patients with CNS metastases.

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