REVIEW

10.2478/AMB-2026-0063

CURRENT THERAPEUTIC APPROACHES TO CEREBRAL METASTASES IN MELANOMA PATIENTS

D. Slavkov[1], P. Troyanova[2], Sv. Troyanova-Slavkova[3]

[1]Department of Neurosurgery, Helios Vogtland Hospital – Plauen, Germany
[2]Department of Oncology, "Tsaritsa Yoanna" University Hospital, Sofia, Bulgaria
[3]Department of Dermatology, Helios Vogtland Hospital – Plauen, Germany

Abstract. *Brain metastases from melanoma (MBMs) present significant treatment challenges due to their aggressive nature and the complexity of managing both intracranial and extracranial disease. Advances in systemic therapies, including immune checkpoint inhibitors (ICIs) and targeted agents, such as BRAF and MEK inhibitors, have improved outcomes for MBM patients, particularly those with asymptomatic disease. Combination therapies, especially nivolumab plus ipilimumab, have shown higher intracranial response rates and durable control compared to monotherapies. Local treatments, including stereotactic radiosurgery (SRS) and surgical resection, remain vital for managing symptomatic or large lesions and may enhance systemic therapy efficacy when integrated appropriately. Recent evidence suggests synergy between ICIs and radiation, leading to improved tumor control and survival, though risks of radiation necrosis require further study. Despite the decline in whole-brain radiotherapy (WBRT) due to limited survival benefits and cognitive side effects, its role as adjuvant therapy after SRS or surgery continues to be explored. Multidisciplinary approaches tailored to individual patient characteristics are essential to optimize outcomes. Ongoing clinical trials will further clarify the safety and efficacy of combined systemic and local treatment modalities in MBM management.*

Key words: *melanoma brain metastases, immune checkpoint inhibitors, BRAF inhibitors, MEK inhibitors, stereotactic radiosurgery, surgical resection, whole-brain radiotherapy, combination therapy*

Corresponding author: *Dr. med. Svetoslava Troyanova-Slavkova, Klinik für Hautkrankheiten und Allergologie HELIOS Vogtland-Klinikum Plauen GmbH 08505 Plauen, Germany, tel.: 03741/49 12422, email: svetoslava.slavkova@helios-gesundheit.de*

ORCID: *0000-0002-7677-9749*

Received: *28 August 2025;* ***Revised/Accepted:*** *12 September 2025*

INTRODUCTION

Melanoma is a malignant tumor originating from melanocytes, which are primarily found in the basal layer of the epidermis. Cutaneous melanoma is the most common form. Besides the skin, melanoma can also arise on other sites such as the uvea, the gastrointestinal tract, the urogenital system, and the meninges. Ultraviolet (UV) radiation, whether from sunlight or tanning beds, remains the primary risk factor for the development of melanoma [1]. Risk of the development of melanoma can depend on the number and type of nevi (moles) and geographic location, and is usually higher in male patients and in Caucasian patients [1]. Although melanoma is less common than other types of skin cancer, it is the deadliest one due to several factors, such as diagnostic challenges, rapid tumor growth, a high

propensity for metastasis, and resistance to treatment. In 2023, there were 324,635 new cases of melanoma worldwide, with 57,043 deaths reported [2].

Melanoma is the third most frequent cause of brain metastases after lung and breast cancers [3]. Up to 60% of patients with advanced melanoma develop brain metastases, which significantly worsens their prognosis. Before the introduction of novel therapies, the median survival for these patients was less than six months [4]. Brain metastases are more common in male patients, and risk factors for them include deep invasion of the primary tumor, elevated lactate dehydrogenase (LDH) levels, tumor localization in the head and neck region, and involvement of lymph nodes or other organs. Approximately 80% of brain metastases are supratentorial and are often multiple, causing complications, such as hemorrhages and seizures [4].

While brain metastases remain the most common and well-characterized CNS involvement in melanoma, rare and severe complications, such as spinal cord involvement, must also be recognized due to their potential for acute and debilitating outcomes. A recent case reported by Gaydarski et al. [5] Described a patient presenting with acute paraplegia caused by a primary spinal melanoma involving both intramedullary and extramedullary compartments. Due to the tumor's atypical location and non-specific clinical features, including pain and progressive motor deficits, the diagnosis was significantly delayed. MRI findings were inconclusive, particularly in amelanotic subtypes, underscoring the need for histopathological confirmation. Although spinal melanomas represent a minority of CNS melanomas, their aggressive nature and potential to mimic more common spinal tumors (e.g., ependymomas, astrocytomas, or lymphomas) pose serious diagnostic challenges [5].

Diagnostic and management challenges in neurosurgical and oncologic practice are often heightened by the complex anatomical locations and aggressive nature of certain tumors and infections. For example, meningiomas at the craniovertebral junction present unique difficulties due to their proximity to critical structures, such as the brainstem, spinal cord, and cranial nerves. These tumors may manifest with subtle and non-specific neurological signs, requiring a high degree of clinical suspicion and advanced neuroimaging, such as MRI, for early detection and precise surgical planning [6]. Similarly, invasive infections like rhino-maxillary mucormycosis (RMM) pose urgent diagnostic challenges, where radiographic modalities, including cone beam computed tomography (CBCT), are essential to delineate the extent of fungal invasion and involvement of adjacent vital structures. Timely identification of RMM is critical given its rapid progression and life-threatening potential [7]. Together, these examples underscore the complexities involved in diagnosing and managing lesions in anatomically sensitive regions and the necessity for multidisciplinary approaches to optimize patient outcomes.

Significant progress has been made in the last decade due to advances in immunohistochemistry and genetic analysis, which have improved diagnosis and guided therapeutic decisions. Melanoma is characterized by a high mutational burden and strong immunogenicity, with over 20 genes implicated in disease progression. The most common mutations occur in the BRAF, NRAS, and KIT genes [8]. The most frequent genetic mutations found in melanoma are BRAF mutations, present in 40–60% of cases, and NRAS mutations, found in approximately 25%. Tumor suppressor genes, such as PTEN and p16, are also commonly altered. Loss of PTEN leads to overactivation of the PI3K/AKT/mTOR signaling pathway, which enhances tumor growth and invasiveness, particularly in the presence of astrocytes that secrete microRNA-containing exosomes [8]. The PI3K/AKT/mTOR pathway stimulates tumor growth, angiogenesis, and metastasis. Astrocytes further activate this pathway by secreting interleukins, such as IL-6 and IL-8, neurotrophins, and granulocyte-colony stimulating factor (G-CSF). Overexpression of the CCR4 receptor increases both the number and aggressiveness of brain metastases by binding to chemokines CCL17 and CCL22 secreted by astrocytes and microglia [8].

Melanoma metastases reach the brain via the bloodstream and must overcome the blood-brain barrier (BBB), a complex structure composed of endothelial cells, pericytes, and astrocytes [8]. Melanoma cells disrupt the BBB by secreting enzymes, such as matrix metalloproteinase-9 (MMP-9) and heparanase, as well as molecules like vascular endothelial growth factor (VEGF), angiopoietin-2, and integrins. After crossing the BBB, metastatic cells initially accumulate around blood vessels and subsequently form tumors [9].

The brain microenvironment is generally hostile to metastases. However, some cells, such as astrocytes, can promote metastatic growth. Amyloid beta protein (Aβ), a peptide closely associated with Alzheimer's disease, activates astrocytes, which protect tumor cells from immune attacks by microglia. Melanoma cells appear to require amyloid beta (Aβ) for survival and growth within the brain parenchyma. These cells degrade amyloid precursor protein (APP) to produce and secrete Aβ. The amyloid beta secreted by the tumor cells stimulates local astrocytes to adopt a pro-metastatic, anti-inflammatory phenotype. Additionally, amyloid beta promotes the anti-inflammatory polarization of microglia and protects melanoma cells from phagocytosis by microglia. Targeting Aβ production through pharmacological inhibition of β-secretase activity may represent a potential therapeutic strategy [10].

The aim of this study is to review the current clinical research regarding the treatment of brain metastases from melanoma, with a focus on evaluating different therapeutic approaches and potential combination strategies.

Management of brain metastases from melanoma

The management of brain metastases from melanoma should be conducted by a multidisciplinary team comprising oncologists, neurosurgeons, radiologists, and neurologists to ensure comprehensive patient care. Surgical resection is recommended for patients with a solitary or limited number of brain metastases who have good functional status, particularly when symptomatic lesions or large tumor volumes are present [11]. Postoperative adjuvant radiotherapy is often administered to achieve local disease control. Stereotactic radiosurgery (SRS) is effective for small to medium-sized metastases, typically up to 3–4 cm, and for patients with a limited number of brain lesions, usually one to four. It is preferred for patients with good performance status and without widespread intracranial disease [11]. Whole brain radiotherapy (WBRT) is less commonly employed in melanoma due to the tumor's relative radioresistance and the risk of adverse effects. It is typically reserved for cases with multiple brain metastases or when other therapeutic modalities are not feasible.

Systemic therapy of brain metastases from melanoma

Systemic therapy plays a crucial role in the management of brain metastases from melanoma. Immunotherapy with the combination of immune checkpoint inhibitors, such as nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4), represents the standard of care, especially for asymptomatic patients, and has demonstrated significant efficacy and prolonged survival [12]. Immune therapy consists of monoclonal antibodies targeting proteins, such as PD-1, a protein expressed on T-lymphocytes, PD-L1, a ligand found on the surface of tumor cells, and CTLA-4, which suppresses T-cell activity. The goal of this therapy is to restore the immune response against the tumor by preventing the suppression of T-cells by cancer cells. Historically, James Allison and his team demonstrated that blocking CTLA-4 leads to tumor regression in mice, which paved the way for the approval of the first drug for metastatic melanoma, ipilimumab, by the FDA in 2011.

For patients without the BRAF V600 mutation, immunotherapy is the first-line treatment. Targeted therapy is indicated for patients harboring the BRAF V600 mutation. BRAF inhibitors, including vemurafenib and dabrafenib, combined with MEK inhibitors, such as trametinib and cobimetinib, have shown activity against intracranial metastases. Combination strategies involving immunotherapy and targeted agents are under investigation and have shown promising preliminary results [13].

Summary of recent clinical trials on therapeutic approaches for melanoma brain metastases

Recent clinical studies have provided valuable insights into the treatment of brain metastases from melanoma, focusing primarily on immunotherapy, targeted therapy, and combination approaches (Table 1).

The very first prospective clinical trial evaluating an immune checkpoint inhibitor in patients with melanoma brain metastases (MBMs) was a two-arm phase II study of ipilimumab [14]. This study comprised two patient cohorts, with cohort A enrolling 51 individuals with asymptomatic MBMs and cohort B including 21 patients who had symptomatic MBMs on a stable steroid regimen. Patients received four doses of high-dose ipilimumab (10 mg/kg) every three weeks, and those demonstrating clinical benefit went on to receive maintenance therapy every 12 weeks. The immune-related complete response rate (ICRR) was 16% in cohort A and 5% in cohort B, with intracranial progression-free survival (iPFS) of 1.9 months and 1.2 months, respectively. A subsequent randomized phase III trial compared high-dose ipilimumab to the FDA-approved dosage (3 mg/kg) in asymptomatic MBM patients and found similar median overall survival – 7.0 versus 5.7 months. Importantly, this larger study revealed a greater survival benefit from high-dose ipilimumab in MBM patients (hazard ratio 0.71) compared to those without brain metastases (hazard ratio 0.92), while no new or unexpected toxicities were observed [15].

Single-agent immune checkpoint inhibitors targeting PD-1, such as pembrolizumab and nivolumab, have demonstrated improved objective response rates, progression-free survival, and overall survival in melanoma patients without brain metastases, along with a more favorable toxicity profile compared to ipilimumab. Pembrolizumab was evaluated in a phase II post-approval study focusing on asymptomatic MBMs and demonstrated an ICRR of 26%, a median progression-free survival of two months, and a median overall survival of 17 months. Similarly, single-agent nivolumab was assessed in the Australian Brain Collaboration study, achieving an ICRR of 20% in asymptomatic, untreated MBM patients, yet only 6% in patients with symptomatic or previously treated lesions. Despite the heterogeneous nature of these trials, monotherapy with immune checkpoint inhibitors consistently produces around a 20–25% ICRR in asymptomatic MBM patients, with nearly all responses proving durable for more than two years [15].

Combination immunotherapy has shown even greater promise. In the phase II CheckMate 204 trial, patients received ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) administered concurrently every three

Table 1. Summary of clinical trial outcomes for melanoma brain metastases treatments

Trial/Study	Treatment	Patient Population	Intracranial Response Rate (ICRR)	Median iPFS (months)	Median OS (months)	Notes/Toxicity
Phase II ipilimumab [14]	Ipilimumab 10 mg/kg	Cohort A: asymptomatic MBM (n = 51)	16%	1.9	-	Cohort B (symptomatic MBM, n = 21). ICRR 5%, iPFS 1.2 months. Maintenance is given if there is clinical benefit.
Phase III ipilimumab [15]	Ipilimumab 10 mg/kg vs 3 mg/kg	Asymptomatic MBM	-	-	7.0 vs 5.7	High-dose showed better survival benefit in MBM vs non-brain mets. No new toxicities have been reported.
Pembrolizumab Phase II [15]	Pembrolizumab	Asymptomatic MBM	26%	2.0	17	Post-approval study. A favorable toxicity profile.
Australian brain collaboration [15]	Nivolumab	Asymptomatic untreated MBM	20%	-	-	Symptomatic or treated lesions: 6% ICRR
CheckMate 204 Phase II [15]	Ipilimumab (3 mg/kg) + nivolumab (1 mg/kg)	Asymptomatic MBM (n = 101)	54%	Not reached	Not reached	84% responses are durable at 3 years. Symptomatic cohort ICRR 17%; maintenance of nivolumab
Phase II NCT02374242 [16]	Ipilimumab + Nivolumab	MBM patients	46%	-	-	17% complete responses. > 50% severe toxicities
NIBIT-M2 Phase III [17]	Nivolumab + ipilimumab vs ipilimumab + fotemustine vs fotemustine	Asymptomatic MBM	44.4%/19.2%/0%	-	29.2/8.2/8.5	The combination showed longest OS. No new toxicities have been reported, but higher overall toxicity has been found.
Phase II (ongoing) [18]	Nivolumab + relatlimab	Asymptomatic MBM (trial ongoing)	-	-	-	Approved for stage IV melanoma but excluded untreated MBM. The study is ongoing.
BREAK-MB Phase II [19]	Dabrafenib	Asymptomatic MBM, treatment naïve or pre-treated	31-39%	3.8	~7.5	Comparable iPFS and OS in both groups
Vemurafenib studies [20]	Vemurafenib	Symptomatic and asymptomatic MBM	16-18%	~3.9	5.3 (symptomatic)	Mo*DES*t response in symptomatic patients. No unexpected toxicities have emerged.
COMBI-MB Phase II [21]	Dabrafenib + trametinib	MBM (symptomatic and asymptomatic)	44-59%	4.2-7.2	10.2-24.3	Lower response and shorter iPFS in steroid users. Intracranial responses are shorter than the extracranial ones.
TRICOTEL Trial [22]	Atezolizumab + vemurafenib + cobimetinib	Untreated, BRAF-mutant MBM	42%	5.3	-	40% symptomatic; median duration of response 7.4 months.
SECOMBIT Trial [23]	Sequential targeted and immunotherapy	BRAF-mutant melanoma	-	-	Comparable survival	Sequential treatment showed similar 2- and 3-year survival rates. No new serious toxicities have been detected.
Phase III Sequence Trial [24]	Nivolumab + ipilimumab → BRAF/MEKi vs reverse	BRAF-mutant melanoma	-	-	71.8% vs 51.5% (2-year OS)	Starting with immunotherapy gave a superior survival prognosis compared to starting with targeted therapy.

weeks for four doses, with ongoing maintenance therapy using nivolumab (3 mg/kg every two weeks) for those who tolerated the regimen and derived benefit [15]. Among 101 asymptomatic MBM patients, the ICRR reached 54%, and long-term follow-up indicated that 84% of these responses persisted at three years post-treatment. At a median follow-up of 34 months, the median intracranial progression-free survival, duration of response, and overall survival had not yet been reached. Following these results, the study added a cohort of 18 symptomatic MBM patients (including those receiving up to 4 mg/day of dexamethasone), who achieved a lower ICRR of 17% but experienced durable responses.

The combination of nivolumab and ipilimumab has demonstrated superior efficacy in another phase II study (NCT02374242) with a 46% intracranial response rate and 17% complete remissions [16]. However, this combined treatment is associated with a higher incidence of adverse effects, including severe toxicities in over half of the patients. The CheckMate 204 trial further confirmed these findings, whereas symptomatic patients had significantly lower response rates and survival.

The NIBIT-M2 phase III trial compared nivolumab plus ipilimumab, ipilimumab plus fotemustine, and fotemustine alone in asymptomatic MBM patients [17]. Intracranial response rates were 44.4% for nivolumab plus ipilimumab, 19.2% for ipilimumab plus fotemustine, and 0% for fotemustine alone. Moreover, median overall survival was significantly longer in the combination arm (29.2 months versus 8.2 and 8.5 months, respectively). Consistent with earlier findings, no unexpected or new toxicities emerged from the combination therapy, although overall toxicity rates were higher compared to monotherapies.

Another immune checkpoint inhibitor combination – nivolumab plus relatlimab – has been approved for stage IV melanoma, based on a phase III trial that excluded patients with untreated MBMs. A phase II study is currently underway to assess its safety and efficacy in asymptomatic MBM patients [18].

Overall, combined immunotherapy targeting both PD-1 and CTLA-4 pathways is considered the most effective option, particularly for patients without neurological symptoms. Treatment individualization based on mutation status, symptom presence, and overall health is essential, and new therapeutic strategies are urgently needed for symptomatic patients due to their poorer outcomes.

Regarding targeted therapies, approximately half of metastatic melanoma patients harbor the BRAF-V600E mutation. BRAF and MEK inhibitors, such as vemurafenib, dabrafenib, and trametinib, have shown superior efficacy over chemotherapy and demonstrate activity against brain metastases. Combination regimens of targeted therapy with immunotherapy offer rapid and durable responses.

Several non-randomized studies have examined both single-agent BRAF inhibitors (BRAFi) and BRAF/MEK inhibitor combinations in patients with BRAF V600-mutant melanoma brain metastases. Early trials focused on single-agent BRAFi. The phase II BREAK-MB trial assessed dabrafenib in patients with asymptomatic MBMs – either treatment-naïve or previously treated with surgery or radiotherapy [19]. Intracranial response rates (ICRRs) were 39% and 31%, and median intracranial progression-free survival (iPFS) was 3.8 months in both groups. Median overall survival (OS) was around 7.5 months. Similarly, vemurafenib showed lower ICRRs of 18% in both treated and untreated patients, with comparable iPFS and OS.

In patients with symptomatic MBMs, vemurafenib led to a modest 16% ICRR, a median PFS of 3.9 months, and a median OS of 5.3 months. No unexpected toxicities were reported with BRAFi in these studies [20].

The phase II COMBI-MB trial was the first to investigate the BRAFi/MEKi combination (dabrafenib + trametinib) in MBM patients [21]. Across four patient cohorts – including both symptomatic and asymptomatic cases – the ICRRs ranged from 44% to 59%. Median PFS varied between 4.2 and 7.2 months, while OS ranged from 10.2 to 24.3 months depending on BRAF mutation subtype and prior brain-directed therapy. However, intracranial responses were typically shorter than extracranial ones, and about half of the patients experienced brain progression, while extracranial disease remained controlled. Patients requiring steroids at baseline had lower response rates and shorter iPFS.

To improve outcomes, the TRICOTEL trial tested a triple combination of atezolizumab (anti-PD-L1), vemurafenib (BRAFi), and cobimetinib (MEKi) in patients with untreated, BRAF-mutant MBMs [22]. Among 65 participants – including 40% with symptomatic disease – the overall ICRR was 42%, the median duration of response (DOR) was 7.4 months, and the median iPFS was 5.3 months.

Sequential treatment strategies have also been explored, as in the SECOMBIT trial, where different sequences of targeted therapy and immunotherapy yielded comparable two- and three-year survival rates without new serious toxicities, supporting the benefit of sequential administration [23].

A phase III study investigating the optimal therapeutic sequence in BRAF-mutant patients compared initial nivolumab plus ipilimumab, followed by BRAF/MEK inhibitors upon progression, against the reverse sequence [24]. The results indicated superior two-year survival for patients starting with immunotherapy (71.8% versus 51.5%), suggesting that initiating

treatment with immunotherapy followed by targeted therapy, if needed, offers the best clinical outcomes.

Local therapies: surgery and radiation

While many patients with melanoma brain metastases also have extracranial disease, local treatments such as surgery and radiation still play a key role alongside systemic therapies. Historically, whole-brain radiotherapy was widely used, but it has shown limited survival benefit and may cause long-term cognitive side effects. In contrast, stereotactic radiosurgery delivers high doses of focused radiation to tumors while sparing healthy brain tissue, making it a preferred option nowadays.

Clinical trials have shown that SRS combined with WBRT can slightly improve survival and performance status compared to WBRT alone, but also increases the risk of memory loss and other side effects [25]. Despite better control of brain disease with WBRT, many patients now receive SRS alone due to its better safety profile. SRS has proven effective even in patients with multiple brain metastases, up to 10 lesions, offering similar survival and tumor control rates to those with fewer lesions. Local control after SRS remains high, with some tumors even disappearing completely after treatment. A retrospective study focusing on MBM patients treated with SRS found local tumor control rates of 87% at 6 months and 68% at 12 months [26]. Another report showed a 90% local control rate, with 11% of tumors completely disappearing after SRS [27]. The use of adjuvant WBRT following SRS or surgery has also been investigated to prevent new brain metastases. In a phase III trial comparing adjuvant WBRT to observation after SRS or surgery, no significant differences were seen in distant brain control or median overall survival, though WBRT did reduce local failure rates (52% vs 58%). Additionally, trials testing adjuvant SRS to the surgical cavity have shown local control rates ranging from about 70% to 90% [28].

Both laboratory and clinical evidence indicate that immune checkpoint inhibitors may synergize with radiation, even stimulating responses in tumors outside the radiation field. One retrospective analysis suggested that delivering SRS within 30 days of ipilimumab treatment improved local tumor control and overall survival in MBM patients [29]. This was further supported by a meta-analysis of 534 patients, which found that those receiving concurrent SRS and ICI had better one-year survival (65% vs. 52%) and local control (89% vs. 68%) compared to those treated non-concurrently [30]. Despite these promising findings, concerns remain about increased risks of radiation necrosis and side effects that can mimic tumor progression. Ongoing clinical trials, such as NCT03340129, aim to clarify the safety and benefits of combining these treatments [31].

Although surgical removal of MBMs has become less common with the rise of effective and less invasive options, it remains important in certain cases. Surgery is typically considered for large, symptomatic tumors over 3 cm, lesions resistant to radiation and systemic therapy, or when a biopsy is needed for diagnosis. A retrospective review of 355 MBM patients suggested that combining surgery or SRS with systemic treatments can improve overall survival [30]. Another study from a single institution showed that patients who had surgery to remove larger tumors followed by ICI therapy lived longer (median OS 22.7 months) than those treated with ICI alone (10.8 months) or ICI followed by surgery (9.4 months) [32]. These findings highlight the ongoing importance of multidisciplinary approaches and further research in managing MBMs.

CONCLUSION

The management of melanoma brain metastases remains one of the most complex challenges in neuro-oncology and dermato-oncology due to the aggressive nature of the disease, the unique brain microenvironment, and the diversity of available therapeutic options. Over the past decade, systemic treatments, such as immunotherapy and targeted therapy, have revolutionized outcomes for patients with advanced melanoma, yet their optimal use, especially in the context of brain metastases, continues to be refined.

Targeted therapies, primarily BRAF and MEK inhibitors, have shown rapid tumor responses in patients harboring BRAF mutations, resulting in high objective response rates. However, these responses may be short-lived, with progression often occurring within a year. In contrast, immunotherapy typically induces more durable responses and significantly extends progression-free survival (PFS) and overall survival (OS), even though initial response rates may be lower. Recent clinical data indicate that first-line immunotherapy offers a survival advantage over targeted therapy for patients with BRAF-mutated advanced melanoma, including those with brain metastases, underscoring its role as the preferred frontline treatment in many cases [34].

Equally important is the consideration of quality of life (QoL) outcomes during therapy. Health-related quality of life (HRQOL) has become a crucial endpoint in melanoma clinical trials, reflecting the importance of maintaining patients' well-being alongside survival gains. Current data indicate that both immunotherapy and targeted therapies preserve HRQOL at baseline levels throughout treatment, which is encouraging, given their substantial impact on survival. Toxicity profiles remain acceptable with mostly manageable adverse effects, although inconsistencies and methodological limitations in HRQOL reporting highlight the need for more standardized, rigorous assessments to better capture patient experiences and inform clinical decisions [35].

Meanwhile, stereotactic radiosurgery remains a cornerstone in managing brain metastases due to its precision

and ability to spare healthy brain tissue. While single-fraction SRS effectively controls many brain metastases, radioresistant tumors, such as melanoma, present ongoing challenges, showing lower local progression-free survival rates and increased risks of radiation necrosis, particularly in larger lesions. Consequently, fractionated stereotactic radiotherapy (FSRT) has gained attention as a strategy to reduce toxicity while maintaining local control, especially for larger metastases. In parallel, emerging evidence suggests that combining radiotherapy with immunotherapy may have synergistic effects in treating melanoma brain metastases [36]. Radiotherapy not only provides local tumor control, but also potentially enhances systemic anti-tumor immunity by increasing tumor antigen presentation and altering the tumor microenvironment. Clinical data reveal that patients receiving both radiotherapy and immunotherapy show improved overall survival compared to those treated with radiotherapy alone [36]. Despite the growing use of immunotherapy, many patients with melanoma brain metastases continue to receive radiotherapy without concurrent immunotherapy, underscoring the urgent need for prospective trials to refine the timing, dosing, and patient selection for these combination approaches to maximize efficacy while minimizing toxicity.

At the same time, basic and translational research has provided new insights into the biology of MBMs. These studies reveal that MBMs possess unique features that may explain their aggressive behavior, but also expose vulnerabilities that could be targeted with novel therapies. Overall, ongoing research and clinical advances hold promise for improving treatment outcomes and addressing unmet needs in MBM patients, while expanding our understanding of the complex biology of these tumors.

Encouragingly, recent clinical trials have demonstrated the feasibility of including MBM patients, which may speed up the development of new therapies. Before the introduction of new therapies, the average survival for patients with brain metastases was around six months. New systemic treatments, including immunotherapy and targeted therapy, now offer alternatives to the traditional surgery and radiation approaches. Combination immunotherapy using anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) has shown better outcomes compared to monotherapy. The most common mutation in metastatic melanoma is BRAF-V600E, found in about 50% of cases, and these patients respond well to targeted therapy. Studies have also demonstrated promising results when combining immunotherapy (atezolizumab) with targeted therapy (vemurafenib plus cobimetinib).

Despite these advances, treatment-related side effects remain a significant challenge, highlighting the need for further research. Nevertheless, these new systemic therapies have the potential to become the first-line treatment for melanoma brain metastases.

FUTURE DIRECTIONS

Despite advances in the treatment of melanoma patients with symptomatic brain metastasis still face poor outcomes. One major challenge in improving therapy for this group lies in the exclusion of symptomatic MBM patients from many clinical trials due to strict eligibility criteria, such as prohibiting corticosteroid use or active brain metastases [37]. Moving forward, it is essential to design clinical trials specifically tailored to symptomatic MBM patients, allowing for concurrent multimodal therapies and corticosteroid use, to better reflect real-world clinical scenarios and improve outcome relevance.

A critical area of investigation is the reduction or avoidance of corticosteroids, which are commonly used to manage vasogenic edema but have well-known toxicities and can impair immune function. Corticosteroid use before or during immune checkpoint inhibitor therapy is associated with worse outcomes, possibly by hindering T-cell responses.

Adoptive cell therapies, including tumor-infiltrating lymphocytes (TILs) and natural killer (NK) cell therapies, offer promising avenues, particularly for patients resistant to conventional immunotherapies. Early-phase trials indicate potential benefits even for patients with brain metastases, although these approaches require further validation [38].

Further understanding of the unique biology of MBM may unlock new therapeutic targets. For instance, enrichment of mutations in PTEN and CDKN2A, and activation of the PI3K/AKT pathway in brain metastases, suggest that targeting these molecular alterations could offer new treatment options less affected by corticosteroid use [38].

Additionally, intracranial tumor burden – especially larger lesions (≥ 2 cm) – has been shown to significantly impact response to immunotherapy and progression risk. This underlines the importance of integrating local therapies, such as surgery or SRS, earlier in treatment to control edema-inducing lesions and improve outcomes [38]. Understanding lesion-specific responses and mechanisms of tumor escape will be key for optimizing combined systemic and local approaches.

In summary, future efforts should focus on:

- Designing inclusive clinical trials tailored to symptomatic MBM patients, allowing multimodal treatment and corticosteroid use.
- Developing strategies to minimize corticosteroid exposure to preserve immune responses.
- Exploring and validating novel immune and targeted therapies, such as adoptive cell therapies and PI3K pathway inhibitors.
- Combining systemic immunotherapies with local treatments early, especially for larger tumors, to improve intracranial control and survival.

These directions hold promise for overcoming current obstacles and improving the prognosis of patients with melanoma brain metastases.

Conflict of Interest Statement: *The authors declare no conflicts of interest related to this work.*

Funding: *The authors did not receive any financial support from any organization for this research work.*

Acknowledgement: *The paper has not been published and/or submitted for publication elsewhere.*

REFERENCES

1. Tchernev G, Oliveira N, Kandathil LJ, et al. Personalised one step melanoma surgery and the outdated/current guidelines for surgical treatment of cutaneous melanoma: Facts and Controversies. Acta Medica Bulgarica, 2022, 49(2): 51-58..
2. Long GV, Swetter SM, Menzies AM, et al. Cutaneous melanoma. Lancet., 2023, 402(10400):485-502.
3. Boire A, Brastianos PK, Garzia L, Valiente M. Brain metastasis. Nat Rev Cancer., 2020, 20(1):4-11.
4. Caulfield JI, Kluger HM. Emerging Studies of Melanoma Brain Metastasis. Curr Oncol Rep., 2022, 24(5):585-594.
5. Gaydarski L, Kolev D, Popov D, et al. Spinal Complications of Melanoma: A Case of Acute Paraplegia. Cureus, 2024, 16(10): e71676.
6. Mitrovic V, Bascarevic V, Stolic R. Foramen magnum meningioma with atypical clinical presentation: a case report. Acta Medica Bulgaria, 2025, 52 (s1): 56-60.
7. Jain Y, Ajila V, Babu GS, et al. Rhinomaxillary mucormycosis impersonating as chronic osteomyelitis: a rare case report with cone beam computed tomography as diagnostic aid. Acta Medica Bulgaria, 2025, 52 (s1): 89-93
8. Colombino M, Casula M, Paliogiannis P, et al. Heterogeneous pathogenesis of melanoma: BRAF mutations and beyond. Crit Rev Oncol Hematol., 2024, 201:104435.
9. Hasanov M, Acikgoz Y, Davies MA. Melanoma Brain Metastasis: Biology and Therapeutic Advances. Hematol Oncol Clin North Am., 2024, 38(5):1027-1043.
10. Kleffman K, Levinson G, Rose I, et al. Melanoma-Secreted Amyloid Beta Suppresses Neuroinflammation and Promotes Brain Metastasis. Cancer Discov., 2022, 12(5):1314-1335.
11. Fonkem E, Uhlmann EJ, Floyd SR, et al. Melanoma brain metastasis: overview of current management and emerging targeted therapies. Expert Rev Neurother., 2012, 12(10):1207-15.
12. Bechev K, Stoitsev Ts, Markov D, et al. HYPERLINK "https://journals.mu-sofia.bg/index.php/amb/article/view/214" A rare neurosurgical challenge:brain meningioma with epidural hematoma.Acta Medica Bulgarica, 2025, 52 (1): 24-30.
13. Queirolo P, Spagnolo F, Ascierto PA, et al. Efficacy and safety of ipilimumab in patients with advanced melanoma and brain metastases. J Neuro Oncol, 2014, 118(1): 109-116.
14. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. J Clin Oncol, 2022, 40(2):127-137.
15. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med, 2018, 379(8):722-730.
16. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol., 2018, 19(5):672-681.
17. Di Giacomo AM, Chiarion-Sileni V, Vecchio M, et al. Nivolumab plus ipilimumab in melanoma patients with asymptomatic brain metastases: 7-year outcomes and quality of life from the multicenter phase III NIBIT-M2 trial. Eur J Cancer, 2024, 199:113531.
18. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma N Engl J Med, 2022, 386(1): 24-34.
19. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol, 2012, 13(11):1087-1095.
20. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol, 2017, 28(3):634-641.
21. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAF(V600) -mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol, 2017, 18(7): 863-873.
22. Dummer R, Queirolo P, Gerard Duhard P, et al. Atezolizumab, vemurafenib, and cobimetinib in patients with melanoma with CNS metastases (TRICOTEL): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol, 2023, 24(12): e461-e471.
23. Ascierto PA, Mandalà M, Ferrucci PF, et al. Sequencing of Ipilimumab Plus Nivolumab and Encorafenib Plus Binimetinib for Untreated BRAF-Mutated Metastatic Melanoma (SECOMBIT): A Randomized, Three-Arm, Open-Label Phase II Trial. J Clin Oncol., 2023, 41(2):212-221.
24. Franken MG, Leeneman B, Gheorghe M, et al. A systematic literature review and network meta-analysis of effectiveness and safety outcomes in advanced melanoma. Eur J Cancer., 2019, 123:58-71.
25. Vasilev P, Ramadan S, Yordanova I, et al. Erythema multiforme-like eruption induced after immune checkpoint inhibitor and target tgerapy in a patient with malignant melanoma- a case report. Acta Medica Bulgarica. Sciendo, 2025, 52 (s1): 50-55
26. Bernard ME, Wegner RE, Reineman K, et al. Linear accelerator based stereotactic radiosurgery for melanoma brain metastases. J Cancer Res Therapeut, 2012, 8(2): 215-221.
27. Mori Y, Kondziolka D, Flickinger JC, et al. Stereotactic radiosurgery for cerebral metastatic melanoma: factors affecting local disease control and survival Int J Radiat Oncol Biol Phys, 1998, 42(3): 581-589.
28. Hong AM, Fogarty GB, Dolven-Jacobsen K, et al. Adjuvant whole-brain radiation therapy compared with observation after local treatment of melanoma brain metastases: a multicenter, randomized phase III trial. J Clin Oncol, 2019, 37:(33): 3132-3141.
29. Skrepnik T, Sundararajan S, Cui H, et al. Improved time to disease progression in the brain in patients with melanoma brain metastases treated with concurrent delivery of radiosurgery and ipilimumab. OncoImmunology, 2017, 6(3): e1283461.
30. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data. Radiother Oncol, 2019, 130:104-112.
31. Phillips WJ, Baghai T, Ong M, et al. Contemporary Report of Clinical Outcomes in Patients with Melanoma Brain Metastases. Curr Oncol., 2021, 28(1):428-439.
32. Tio M, Wang X, Carlino MS, et al. Survival and prognostic factors for patients with melanoma brain metastases in the era of modern systemic therapy. Pigment Cell Melanoma Res, 2018, 31(4):509-515.
33. Alvarez-Breckenridge C, Giobbie-Hurder A, Gill CM, et al. Upfront surgical resection of melanoma brain metastases provides a bridge toward immunotherapy-mediated systemic control. Oncol, 2019, 24(5):671-679.
34. Sun C, España S, Richarz N, et al. Targeted therapy or immunotherapy in BRAF-mutated metastatic melanoma: a Spanish center's decade of experience. Front Oncol., 2024, 14:1322116.
35. Chen C, Wang Z, Qin YR. Health-related quality of life in stage III-IV melanoma treated with targeted therapy or immunotherapy: A systematic review on the adequacy of reporting and clinical issues in phase III randomized controlled trials. Cancer Med., 2023, 12(3):2262-2280.
36. Gruber I, Weidner K, Treutwein M, Koelbl O. Stereotactic radiosurgery of brain metastases: a retrospective study. Radiat Oncol., 2023, 18(1):202.
37. Knox A, Wang T, Shackleton M, Ameratunga M. Symptomatic brain metastases in melanoma. Exp Dermatol., 2024, 33(4):e15075.
38. Tringale KR, Reiner AS, Sehgal RR, et al. Efficacy of immunotherapy for melanoma brain metastases in patients with concurrent corticosteroid exposure. CNS Oncol., 2023, 12(1):CNS93.