The role of systemic therapy in melanoma brain metastases: a narrative review

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Background and Objective: Melanoma is a disease notorious for the development of brain metastases, with consequently poor outcomes for patients who develop melanoma brain metastases (MBM). The treatment options for patients with MBM were limited to radiotherapy and surgery. MBM patients, particularly those with symptomatic disease, were excluded from clinical trials of immune checkpoint inhibitors (ICI) and BRAF/MEK inhibitors. Recent post-approval studies have, demonstrated important roles for existing systemic ICIs and BRAF/MEK inhibitors in untreated MBM, dramatically altering the landscape of melanoma patients in general and MBM in particular. These trials have also identified key areas for which more effective strategies are needed including: symptomatic MBM, and leptomeningeal disease (LMD).

Methods: PubMed, Scopus and Embase databases were systematically queried to obtain records pertaining to the etiology of and treatment for MBM. Clinical trial databases were reviewed to obtain details regarding MBM clinical trials.

Key Content and Findings: We discuss the etiopathogenesis of MBM and the novel immune, molecular and metabolic features of MBM that make this disease a unique therapeutic challenge. We review advances in systemic therapy with ICIs and BRAF/MEK inhibitors in untreated MBM, along with novel combinations. Finally, we debate challenging situations such as LMD, and delineate novel treatments and new paradigms for therapeutic interventions.

Conclusions: The historically poor outcomes for MBM patients have been transformed with the advent of effective systemic therapies including ICIs and BRAF/MEK inhibitors. An improved understanding of the molecular and immunogenomic characterization of MBMs has provided new targets that are being exploited in the clinic.

Keywords: Melanoma; melanoma brain metastases (MBM); immunotherapy; targeted therapy; immune checkpoint inhibitors (ICI); programmed death-1 (PD-1); CTLA-4; BRAF; MEK

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Introduction

Cutaneous melanoma exhibits the highest level of cerebral tropism of all cancer types, with up to 30–40% of advanced melanoma patients having melanoma brain metastases (MBM) at diagnosis (1-3), and up to 75% at the time of death in autopsy series (2). MBM are associated with a higher risk of complications and death compared to other cancers (4,5). While surgical resection and stereotactic radiosurgery (SRS) are highly effective for local control

of oligometastatic MBM (2,6), patients with multiple brain metastases and/or leptomeningeal disease (LMD) are typically treated with whole-brain radiation therapy (WBRT) with poor outcomes. The prognosis of MBM patients has remained poor, with a median overall survival (OS) of 4–5 months, and a durable survival rate of 5% (6).

Historically, patients with untreated brain metastases were excluded from clinical trials for all currently approved targeted and immune therapies given the uncertain penetrance of the blood-brain barrier (BBB) by systemic agents and consequent perceived uncertainties over central nervous system (CNS) efficacy. Several post-marketing clinical trials subsequently clarified that immune checkpoint inhibitors (ICI) and small molecules targeting BRAF and MEK kinases had intracranial activity in MBM patients. These trials also identified key areas for which more effective strategies are needed. Concurrently, recent translational and preclinical research have provided insights into novel immune, molecular and metabolic features of MBM that mediate the aggressive biology and therapeutic resistance of these tumors. In this systematic review, we review the etiopathogenesis of MBM, and describe the various therapeutics options available with a focus on new paradigms for therapeutic interventions in MBM. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-22-1/rc).

Methods

Without imposing any restriction on the publication language and publication time, the PubMed, Scopus and Embase databases were systematically queried to obtain records published before April 1, 2022, with the following keywords: ("melanoma" OR "brain" OR "melanoma brain metastases") and ("epidemiology") and ("tumor microenvironment" OR "TME" or "pathway") and ("targeted therapy" OR "BRAF" OR "MEK") and ("immune therapy" OR "programmed cell death 1" OR "PD-1" OR "PD1" OR "programmed death 1 receptor" OR "cytotoxic T-lymphocyte-associated antigen 4" OR "CD152" OR "CTLA-4") (Table 1). We also used the Emtree terms to increase the sensitivity of our systematic search.

Studies with the following eligibility criteria were included in our study: (I) investigations that studied the effects of targeted or immune therapies on MBM, and (II) studies that described the epidemiology and/or translational molecular immunobiology of MBM. Based on the following criteria, studies were excluded from the current systematic review: (I) studies that did not meet the abovementioned inclusion criteria, (II) review papers, (III) meeting abstracts, (IV) perspectives, (V) book chapters, (VI) editorial articles, (VII) commentaries, (VIII) opinion articles, and (IX) duplicated papers.

Following the systematic search, the records were retrieved and reviewed. Initially, the titles and abstracts of all obtained papers were screened, and those that did not meet criteria were excluded. Subsequently, the full text of all remaining papers and supplementary data were reviewed for consideration to be included in the current study.

The following data were extracted from the included studies: (I) the first author, (II) the year of publication, and (III) the main findings.

Discussion

Epidemiology and etiopathogenesis

Cutaneous melanoma is the third most common cause of metastases to the brain, exceeded only by lung cancer and breast cancer (7). Brain metastases can be seen in patients with non-cutaneous melanoma including mucosal and uveal variants (8,9). However, immunogenomic characterization and translational clinical trial efforts have focused upon cutaneous MBM; hence, we have sought to limit our discussion in this narrative review to MBM arising in the setting of cutaneous melanoma only. Several risk factors are associated with MBM development including male gender, increasing age, primary tumor location (head and neck *vs.* trunk), primary tumor depth (Breslow depth), ulceration of primary tumor, presence of visceral metastases, elevated serum lactate dehydrogenase (LDH) level, and CCR4 expression (10-14). CCR4 PKB/Akt leads to activation of the PI3K pathway (15), and is linked to MBM formation in preclinical models (10,15).

Melanoma cells primarily spread to the brain hematogenously. Under normal circumstances, the brain is a "sanctuary" site protected from external influences by the BBB that comprises endothelial cells connected by tight junctions and surrounded by a basal lamina composed of pericytes and astrocyte endfeet. The BBB is uniquely equipped with special efflux pumps for drugs and has slow rates of transcytosis (16). This complex, multi-layer system limits the entry of pathogens, drugs, and toxins into the CNS, although melanoma cells have unique adaptations that facilitate BBB penetrance. Upon arrival at

the microcapillaries of the brain, they arrest due to their size and remain quiescent (17). Tumor cell extravasation is mediated through various mechanisms: (I) physical disruption of the BBB by the development of cytoplasmic processes that push endothelial cells apart, (II) loosening of tight junctions through the release of angiopoietin-2 and expression of other pro-invasive integrins by the melanoma cells, and (III) cleavage of the basement membrane of BBB by various proteases expressed by the tumor cells (17,18). After extravasation, tumor cells use the blood vessels as tracks for invasion (vessel cooption) (19). This pattern of invasion explains the higher incidence of MBM in regions of the brain with greater blood flow such as frontal lobes. The immune response to tumor invasion in the brain is also complex. Under homeostatic conditions, the brain is an immune-privileged tissue, and the BBB has low expression of adhesion molecules and low leukocyte traffic (20). However, BBB disruption by tumor cells results in increased penetration of CNS by lymphocytes which may be responsible for the unique microenvironment of MBM (21-23).

MBM tumor microenvironment (TME) and role of PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways in MBM

While the TME of MBMs is heterogenous, subgroups differentially enriched in T cells, monocytes and myeloid dendritic cells with commensurately altered survival can be identified (24). The immune infiltrate of MBMs comprises a mixed population of tumor-infiltrating lymphocytes (TILs), and the TIL density in MBM is the highest of all solid tumor CNS metastases (25). Paired analyses of intra- and extra-cranial metastases reveals that the TME of MBMs is significantly enriched with macrophages and gamma delta T cells (γδ T cells), although the frequency of NK cells is reportedly lower in MBM compared to matched primary tumors (23,26).

The genetics of MBM are similar to other systemic metastatic sites of melanoma: activating point mutations in *BRAF* are found in 42–50% of MBM, while other driver mutations include *NRAS* (15–28%), and *NF1* (22%) (27,28). However, MBM is uniquely characterized by oncogenic activation of the PI3K-AKT pathway (29,30), typically through loss of function mutations in the tumor suppressor gene *PTEN*, found in 20–30% of melanoma and typically associated with concurrent activating mutations in *BRAF* (31,32). PI3K/AKT pathway activation facilitates MBM development via upregulation of CCR4, heparanase, VEGF, and STAT3 (15,33,34), and PTEN loss is an adverse prognostic factor in MBM (35).

Recent work has shed light on the role of tumor-intrinsic metabolism on the development and response of MBM to ICIs and targeted therapy. Compared to extracranial metastases and primary melanomas, gene expression and metabolite profiling reveal that MBMs demonstrate increased oxidative phosphorylation (OXPHOS), in turn associated with lower immune infiltrates and reversed, in preclinical studies by addition of direct OXPHOS inhibitor IACS-010759 (24). OXPHOS induction appears to occur secondary to a shift in nutrient dependence from glucose to other amino acids such as glutamine in metastatic cells (36), leading to an upregulation of *de novo* amino acid synthesis to overcome the dearth of extracellular amino acids in the brain—therapy facilitating cerebral tropism, a phenomenon that has been recapitulated in brain metastases from multiple tumor types (37).

Systemic therapy in MBM

Optimal management of MBM requires a multidisciplinary approach that considers all available treatment modalities that balances the factors that need to be considered in determining a comprehensive treatment approach including: nature of brain disease (number and size of metastases, location of metastases, presence or absence of neurological symptoms and presence or absence of LMD), extracranial disease burden, tumor mutation status (*BRAF* mutant or wildtype), patient's functional status, and prior therapy for MBM. In addition, the context of MBM development (i.e., MBM development prior to *vs.* while on systemic therapy) also helps determine the order of local and systemic therapy. There remain clear roles for radiation therapy (38-40), and surgery (41) in the management of MBM, but these are well-discussed elsewhere. Below, we focus on the systemic therapy options for MBM patients.

Principles of systemic therapy

Historically, patients with untreated MBM were excluded from systemic therapy clinical trials due to concerns about CNS drug penetrance, neurotoxicity and poor prognosis (42,43). In the context of untreated MBM, several case reports unexpectedly suggested that both ICIs and targeted BRAF/MEK had intracranial efficacy. These led to formal phase II studies evaluating BRAF/MEK targeted therapy

and ICIs in patients with untreated MBM that are further elaborated upon below. The majority of these studies had fairly stringent criteria, and limited patients based on size of MBM (0.5–3.0 cm), degree of symptoms (asymptomatic or minimally symptomatic), and systemic glucocorticoid use (absent or minimal) due to concerns over rapid disease progression in symptomatic patients (44), and lack of efficacy with concomitant steroid use particularly in patients treated with ICIs (45). LMD was and remains a poorly studied population, and these patients continue to be excluded from clinical trials.

The use of ICIs in MBM

Programmed death-1 (PD-1) is a receptor expressed by activated T cells which binds to programmed death ligand 1 (PD-L1, B7-H1) (46,47), and PD-L2 (B7-DC) (48,49). PD-1 negatively regulates T cell function primarily through the engagement of PD-L1, which is expressed by a wide variety of tissues (46-49) and human tumors, including melanoma, either constitutively or after treatment with IFN-γ (50,51).

Separately, cytotoxic T lymphocyte associated antigen-4 (CTLA-4, CD152) is an activation-induced glycoprotein that belongs to the Immunoglobulin (Ig) superfamily. CTLA-4 is homologous to the T cell co-stimulatory protein CD28; but where CD28 provides the co-stimulatory signal required for antigen-specific T cell activation and expansion after the initial interaction between T cell receptor (TCR) and antigen presenting cells (APCs), CTLA-4 down-regulates T cell responses by acting as a decoy receptor (52-54). CTLA-4 is constitutively expressed on regulatory T cells (Tregs) while expression on $CD8^+$ T cells occurs rapidly following TCR engagement (signal 1) (55,56). Both CD28 and CTLA-4 have two natural ligands found on APCs: CD80 (B7.1) or CD86 (B7.2) (57-59), although CTLA-4 has higher avidity and affinity for both compared to CD28 (60-62). Because B7.1/B7.2 provide the positive costimulatory signal (signal 2) through CD28 required for TCR activation, competitive inhibition of CD80 and CD86 by CTLA-4 effectively attenuates T cell activation. CD80 and CD86 are primarily expressed at sites of T-cell priming (e.g., secondary lymphoid organs), and to a lesser extent constitutively expressed to varying degrees on antigen-presenting cells (APC) and activated T cells. Hence, CTLA-4 blockade primarily increases T cell priming, and secondarily reduces Treg-mediated suppression of T cell responses.

Ex vivo, PD-1/PD-L1 pathway blockade in combination with prolonged antigen stimulation augments the frequencies of cytokine-producing, proliferating tumor antigen (TA)-specific $CD8^+$ T cells which express markers of T cell activation/exhaustion including PD-1 and CTLA-4 (63,64). Separately, CTLA-4 blockade primarily induces expansion of ICOS+ T_h1-like CD4 effector population, and secondarily increases the number of exhausted/activated $CD8^+$ T cells (65). Conversely, combination CTLA-4/PD-1 dual blockade induces distinct changes with increased expression of terminally differentiated $CD8^+$ T cells expressing Tbet and EOMES in addition to the afore noted findings with either PD-1 or CTLA-4 blockade singly (66,67).

ICIs targeting the PD-1/PD-L1 and CTLA-4 pathways have transformed the management of melanoma with approvals in the high-risk node negative, node positive, and metastatic settings. In advanced melanoma, blockade of PD-1 singly or in combination with CTLA-4, results in objective response rate (ORR) of 35–41% (pembrolizumab or nivolumab) (68-72), 43% (nivolumab/relatlimab combination), and 55% (nivolumab-1/ipilimumab-3 combination) (73-77), with grade 3–4 immune-related adverse event (irAE) rates of 10%, 19% and 55% respectively. Dropping the dose of ipilimumab (nivolumab-3/ipilimumab-1 combination) is associated with a lower dose of grade 3–4 irAEs but undiminished efficacy (78).

The first report of clinical efficacy of ICIs in untreated MBMs occurred more than a decade ago in two separate patients with advanced metastatic melanoma (79,80). In both instances, patients with untreated, progressive MBM responded favorably to ipilimumab with systemic and CNS responses (79,80). These results were buttressed by data from an Italian Expanded Access Program (EAP) that evaluated ipilimumab in 146 asymptomatic MBM patients of whom 145 were evaluable for response, and reported global ORR of 11% with durable benefit observed in a subset (81). Interesting developments in these reports that foretold future developments in this arena included the development of edema surround MBM (and consequent need for corticosteroids and anti-epileptic drugs), tumor necrosis, delayed regression of MBM, discordant responses in MBM *vs.* systemic lesions and yet, the possibility of durable benefit in a small subset of treated patients (79-81). These observations led to a plethora of trials, summarized in *Table 2* and described below.

These results led to the formal evaluation of ipilimumab 10 mg/kg in untreated MBM in a phase II single-arm trial (CA184-042) that included 2 cohorts: Cohort A with 51

Table 1 The search strategy summary

Items	Specifications
Date of search (specified to date, month and year)	4/1/2022
Databases and other sources searched	PubMed, Scopus and Embase
Search terms used (including MeSH and free text search terms and filters)	("melanoma" OR "brain" OR "melanoma brain metastases") and ("epidemiology") and ("tumor microenvironment" OR "TME" or "pathway") and ("targeted therapy" OR "BRAF" OR "MEK") and ("immune therapy" OR "programmed cell death 1" OR "PD-1" OR "PD1" OR "programmed death 1 receptor" OR "cytotoxic T-lymphocyte-associated antigen 4" OR "CD152" OR "CTLA-4")
Timeframe	Published until 4/1/2022
Inclusion and exclusion criteria (study type, language restrictions, etc.)	Studies matching the search terms above were included
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All authors
Any additional considerations, if applicable	None

asymptomatic MBM patients who not on corticosteroids, and Cohort B with 21 symptomatic MBM patients maintained on a stable corticosteroid dose (82). The intra-cranial ORR of 16% (Cohort A) and 5% (Cohort B), and median OS of 7.0 months and 3.7 months confirmed the safety and intracranial efficacy of ipilimumab in patients with untreated MBM; but the striking difference in ORR and OS between the two cohorts formed the basis to exclude patients requiring corticosteroids in future MBM trials of ICIs. Given the dose-response relationship observed with ipilimumab at 10 *vs.* 3 mg/kg, this question was tested in a phase III trial (CA184-169) that included 127 patients with asymptomatic untreated MBM where the results confirmed the superiority of ipilimumab 10 mg/kg (over 3 mg/kg) with significantly greater 1-year progression-free survival (PFS). ORR was similarly greater for ipilimumab 10 mg/kg (over 3 mg/kg), although this difference was not statistically significant (83). Subset analyses revealed that MBM patients derived durable benefit that held up at later follow-up (84). Collectively, these studies established a clear paradigm that ICIs were effective in untreated MBM and primed the field for future developments.

The efficacy of anti-PD-1 ICIs in melanoma spurred the evaluation of anti-PD-1 ICI in MBM patients, initially in the setting of a non-randomized phase II trial that studied pembrolizumab in patients with untreated MBM (85). Driven by the prior experiences with ipilimumab, enrollment was limited by size of intra-parenchymal lesion (5–20 mm) and excluded patients who were either symptomatic and/or needed corticosteroids. The intra-cranial ORR was 22% (4/18) in MBM with concordant brain and systemic responses, and updated reporting demonstrated that responses were durable with all intra-cranial responses ongoing at 24 months—statistics that compared favorably to the single-agent ORRs in either disease (86).

Prompted by the development of dual PD-1/CTLA-4 blockade in advanced melanoma, the efficacy of the ipilimumab/nivolumab combination in MBM was evaluated in two clinical trials: CheckMate-204 and ABC (44,87-89) (*Table 2*). CheckMate-204 was a phase II study that evaluated ipilimumab/nivolumab at the approved doses (ipilimumab 1 mg/kg with nivolumab 2 mg/kg every 3 weeks for 4 doses; then nivolumab 2 mg/kg every 2 weeks for 2 years) in two cohorts: Cohort A (101 patients) with asymptomatic brain metastases, and Cohort B (18 patients) with symptomatic disease. In a notable departure from prior studies, the primary endpoint of the trial was an efficacy one—specifically, intracranial clinical benefit rate which was defined as the aggregate sum of patients with complete or partial response, and stable disease lasting at least 6 months. The intracranial clinical benefit rate was greater in cohort A compared to B (57% *vs.* 22%); and while the rate of grade 3/4 adverse events was comparable in both arms, the rate of CNS adverse events was much higher in cohort B (6.9 *vs.* 16.7%) (44,87). Unlike the CheckMate-204 study which evaluated only the ipilimumab/nivolumab combination albeit in asymptomatic and symptomatic MBM, the ABC study compared the ipilimumab/nivolumab combination

Table 2 Completed studies of immune checkpoint inhibitors in MBM

First author; study identifiers	Study design		Patient population			Intervention	Intra-cranial response rate	Extra-cranial response rate	Grade 3/4 AEs
	Cohorts	Sample size	General features of brain disease	BRAF status	Size and No. of target lesions				
Margolin; CA184-042 (NCT00623766)	Cohort A	51	Asymptomatic; no steroid use; prior local therapy	N/A	0.5–3 cm; number N/A	Ipilimumab 10 mg/kg Q3W × 4; then Ipilimumab 10 mg/kg Q12W	16%	14%	62%
	Cohort B	21	Asymptomatic; on systemic steroids; prior local therapy				5%	5%	55%
Ascierto; CA184-169 (NCT01515189)	Arm 1	365 (65 with MBM)	Asymptomatic, not requiring treatment	22% mutant, 62% WT, 16% UNK	N/A	Ipilimumab 10 mg/kg	15%		36%
	Arm 2	362 (62 with MBM)		22% mutated, 65% WT, 13% UNK		Ipilimumab 3 mg/kg	12%		20%
Goldberg; NCT02085070	Single-arm	18 (14 evaluable)	Asymptomatic; with or without prior local treatment	33% mutant	5–20 mm; 1–5 BM per patient	Pembrolizumab 10 mg/kg Q2W	22%	22%	12%
Tawbi; CheckMate-204 (NCT02320058)	Cohort A	101 (94 evaluable)	Asymptomatic; no prior radiotherapy	65.3% mutant, 32.7% WT, 2% UKN	0.5–3.0 cm; 77.2% with 1–2 BM, 22% ≥3 BM	Ipilimumab 3 mg/kg + nivolumab 1 mg/kg Q3W × 4; then nivolumab 3 mg/kg Q2W	54.4%	49%	54.5%
	Cohort B	18	Symptomatic; no prior radiotherapy	44.44% mutant, 44.44% WT, 11% UKN	0.5–3.0 cm; 61% w/1–2 BM, 39% ≥3 BM		22.2%	22.2%	55.6%
Long; ABC (NCT02374242)	Cohort A	36	Asymptomatic; no prior local therapy	54% mutant	0.5–4 cm; 31% w/1 BM, 40% w/>4 BM	Nivolumab 1 mg/kg + ipi 3 mg/kg Q3W X 4; then nivolumab 3 mg/kg Q2W	46%	57%	63%
	Cohort B	27		56% mutant	0.5–4 cm; 24% w/1 BM, 20% w/>4 BM	Nivolumab 3 mg/kg Q2W	20%	29%	16%
	Cohort C	16	Symptomatic or failed local therapy or LMD	81% mutant	0.5–4 cm; 6% w/1 BM, 50% w/>4 BM	Nivolumab 3 mg/kg Q2W	6%	25%	13%
Di Giacomo; NIBIT-M1 (NCT01654692)	Single-arm	86 (20 with MBM)	Asymptomatic; 7 patients with prior radiotherapy	48% mutated; 35% WT; 17% UNK	Size NA; 30% w/1 BM, 15% w/>3 BM	Ipi 10 mg/kg Q3W × 4 + fotemustine 100 mg/m^2 QWeekly × 3; then fotemustine Q3W + ipi Q12W	40%	29%	55%

MBM, melanoma brain metastases; AE, adverse event; N/A, not available; W, weeks; WT, while-type; UKN, unknown; LMD, leptomeningeal disease.

(Cohort A, 36 patients) to nivolumab monotherapy (Cohort B, 27 patients) although the study was not designed for a formal comparison between cohorts. Valuably, the ABC study additionally included a 3rd arm comprising patients with symptomatic MBM, LMD and/or MBM that failed radiation therapy or surgery with a similar primary endpoint (Cohort C, 16 patients) (88,89). The intracranial clinical benefit rate was numerically greater in Cohort A compared to B (46% *vs.* 20%), clearly demonstrating the superiority of the ipilimumab/nivolumab combination in this patient population, even with extended follow-up (89). Conversely, the intracranial clinical benefit rate was very low (6%, 1 patient) in Cohort C, underscoring the limitations of systemic immunotherapy even with dual PD-1/CTLA-4 blockade in this highly-refractory patient population. Concordant with CheckMate-204, the grade 3/4 adverse event rate was high with ipilimumab/nivolumab combination (Cohort A—46%, Cohort B—4%, Cohort C—13%). Collectively, both CheckMate-204 and ABC studies clearly established the efficacy of ipilimumab/nivolumab combination in patients with asymptomatic first-line MBM.

Targeted therapy use in MBM

The commonest oncogenic alterations in melanoma are in *BRAF* codon V600 (40–50%), *NRAS* codons 12, 13, or 61 (15–23%), *NF1* (24%) and *CKIT* (3%) Of these, mutations in the RAF-MEK-ERK MAPK in *BRAF* and *NRAS* are typically seen in in melanomas without chronic sun damage (CSD) compared with those associated with CSD (*BRAF*: 60% *vs.* 6–22%; *NRAS*: 20–22% *vs.* 0–15%), while *KIT* mutations are significantly more common with CSD associated melanomas (15–30% *vs.* <1%) and in patients of Asian descent (90-93). Outside of rare instances or in the setting of acquired resistance following exposure to BRAF (or BRAF/MEK) inhibitor therapy, these driver mutations are typically mutually exclusive. *BRAF* V600E mutations are more common in females, younger patients; while NRAS mutations are commoner in older and male patients (94,95). Targeted kinase inhibitors of both BRAF (vemurafenib, and dabrafenib) and MEK (cobimetinib, and trametinib) demonstrated high radiographic response rates with improved PFS and OS in *BRAF* V600 mutant melanoma (96-98). However, resistance inevitably develops secondary to BRAF inhibitor-induced paradoxical reactivation of MAPK pathway (99-101). Preclinically, combination BRAF and MEK inhibition (vemurafenib/cobimetinib, dabrafenib/trametinib, and encorafenib/binimetinib) enhances the inhibitory effect on MAPK pathway signaling in BRAF mutant cells and delays emergence of resistance (99-101), and clinically is associated with even greater benefit (improved ORR, PFS and OS) compared to BRAF inhibitor monotherapy without a substantial increase in toxicity (102-105).

Similar to the experience with ICIs, the use of BRAF and BRAF/MEK inhibitors in untreated MBM was triggered by several favorable case reports that hinted at intra-cranial efficacy (106,107). These results led to a surfeit of clinical trials evaluating BRAF inhibitors singly and combination BRAF/MEK inhibitors in MBM, summarized in *Table 3*.

Single agent BRAF inhibitor therapy was evaluated in 3 trials: 1 each involving vemurafenib (MO25743) and dabrafenib (BREAK-MB) in asymptomatic MBM, and a separate study that evaluated vemurafenib in symptomatic MBM patients (108-110). Both studies enrolled patients with *BRAF* V600 codon mutant and single or multiple MBM between 0.5–4 cm into separate cohorts depending on prior MBM-directed therapy, although MO25743 permitted LMD that BREAK-MB excluded. The former studies enrolled MBM patients and had relatively similar enrollment criteria: presence of activating *BRAF* V600 codon mutant, single or multiple MBM between 0.5–4 cm. In general, the studies revealed that MBM patients exhibited clinically meaningful response rates to single agent BRAF inhibitors that were well tolerated and without significant CNS toxicity, although unlike with ICIs, the intra-cranial and extra-cranial response rates are not commensurate, with the intra-cranial rates typically lower than the extra-cranial rates, although the reason for this is not clear as the aforenoted CNS penetration of BRAF (and MEK) inhibitors and their efficacy in primary brain tumors including pediatric gliomas and glioblastoma multiforme (111). Of note, single agent vemurafenib demonstrated safety and efficacy in symptomatic MBM, unlike the experience with ICIs as noted earlier (110).

A separate trial (BUMPER) evaluating the CNS-penetrable pan-PI3K inhibitor buparlisib in untreated MBM demonstrated that buparlisib monotherapy produced no intracranial responses in MBM patients unselected for PI3K pathway activation, although the drug itself was well tolerated (112). The MEK inhibitor binimetinib showed modest efficacy in a pilot study of 11 patients with *NRAS* mutated MBM who had failed multiple previous lines of therapy (113). ORR was 18%, although interestingly, in 2 patients, responses were deeper intracranially than

Table 3 Completed studies of BRAF, BRAF/MEK and other targeted therapies in MBM

First author; study identifiers	Study design		Patient population			Intervention	Intra-cranial response rate	Extra-cranial response rate	Grade 3/4 AEs
	Cohorts	Sample size	General features	*BRAF* status	Size and No. of target lesions				
Long; BREAK-MB (NCT01266967)	Cohort A	89	Asymptomatic; no prior local treatment	*BRAF* V600E/K	0.5–4 cm; 46% w/1 BM, 9% w/>4 BM	Dabrafenib 150 mg BID	20%	N/A	14%
	Cohort B	83	Asymptomatic; prior SRS, WBRT or surgical resection with progression		0.5–4 cm; 36% w/1 BM, 17% w/>4 BM		30%	N/A	13%
McArthur; MO25743 (NCT01378975)	Cohort 1	90	No prior local treatment	*BRAF* V600E	≥0.5 cm; 44% w/1 BM, 14% w/>4 BM	Vemurafenib 960 mg BID	18%	33%	66%
	Cohort 2	56	Prior SRS, WBRT or surgical resection with progression. 7% had LMD		≥0.5 cm; 20% w/1 BM, 18% w/>4 BM		18%	23%	64%
Dummer; MO25653 (NCT01253564)	Single-arm	24 (19 evaluable for IC response, 21 for EC response)	Symptomatic *vs.* asymptomatic; failure of one prior line of treatment for brain disease	*BRAF* V600 subtypes N/A	Size N/A; 8% w/1 BM, 54% w/>3 BM	Vemurafenib 960 mg BID	16%	62%	17%
Amaral; BUMPER (NCT02452294)	Single-arm	22 (17 evaluable for response)	Asymptomatic; with or without prior local therapy	*BRAF* V600E/K (53%) *vs. BRAF* WT (43%)	Size N/A; 100% w/>5 BM	Buparlisib 100 mg once daily	0%	0%	12%
Goldinger (NCT record not available)	Single-arm	11	Symptomatic *vs.* asymptomatic; with or without prior systemic and local therapy	*NRAS* mutated	Size N/A; 18% w/1 BM, 46% w/>3 BM	Binimetinib 45 mg BID	18%		55%
Davies; COMBI-MB (NCT02039947)	Cohort A	76	Asymptomatic; no local therapy; ECOG 0, 1	*BRAF* V600E	0.5–4 cm; 54% w/1 BM, 10% w/≥4 BM	Dabrafenib 150 mg BID + Trametinib 2 mg daily	58%	55%	45%
	Cohort B	16	Asymptomatic; prior local therapy; ECOG 0, 1	*BRAF* V600E	0.5–4 cm; 44% w/1 BM, 0% w/≥4 BM		56%	44%	56%
	Cohort C	16	Asymptomatic; with or without prior local therapy; ECOG 0, 1	*BRAF* V600D/K/R	0.5–4 cm; 44% w/1 BM, 6% w/≥4 BM		44%	75%	56%
	Cohort D	17	Symptomatic; with or without prior local therapy; ECOG 0, 1, 2	*BRAF* V600D/E/K/R	0.5–4 cm; 41% w/1 BM, 12% w/≥4 BM		59%	41%	47%

MBM, melanoma brain metastases; AE, adverse event; BM, brain metastases; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy; W, weeks; BID, twice daily; N/A, not available; LMD, leptomeningeal disease; EC, extracranial response; IC, intracranial response; WT, while-type.

extracranially.

Based on the enhanced anti-tumor activity and improved OS of combined BRAF/MEK inhibition compared to BRAF monotherapy alone, combination BRAF/MEK inhibitor therapy became the approved standard for *BRAF* V600 mutant melanoma over BRAF inhibition alone and prompted evaluation in MBM. COMBI-BM evaluated the dabrafenib/trametinib combination in 125 MBM patients in 4 cohorts: *BRAF* V600E mutant asymptomatic, untreated MBM (cohort A); *BRAF* V600E mutant asymptomatic, previously treated MBM (cohort B); *BRAF* non-V600 mutant (V600D/K/R mutant) asymptomatic, previously treated/untreated MBM (cohort C); and *BRAF* non-V600 mutant symptomatic, previously treated/untreated MBM (cohort D) (114). The majority of patients in each cohort had one or two brain metastases and had extracranial metastatic disease at the time of recruitment. The intra-cranial response rates were similar in all cohorts (cohort A 58%; cohort B 56%; cohort C 44%; cohort D 59%), and typically lower than the commensurate extra-cranial response rates (cohort A 55%; cohort B 44%; cohort C 75%; cohort D 41%), underscoring the trend seen with single agent BRAF inhibitor use. Concordantly, the duration of intra-cranial response was typically lower than for extra-cranial response (6.5 *vs.* 10.2 months), which pointed towards early CNS failure with BRAF/MEK inhibition—another distinction *vis* ICI use, wherein intra- and extra- cranial responses were concordant, and responses were typically long-lasting.

Combined TT and ICI therapy in MBM

Preclinical studies demonstrated potential synergies between combined BRAF/MEK inhibition and ICIs for several reasons including:

(I) Increased T cell effector and DC function following combined BRAF/MEK inhibition *in vitro* in co-culture experiments (115-117).

(II) Independent beneficial effects upon multiple components of the tumor immune microenvironment, including increased frequencies and enhanced activation status of TIL, and inhibition of suppressive immune cells including tumor-associated macrophages, and myeloid-derived suppressor cells, and consequent synergy with ICI (118,119).

Based on the above, randomized phase II trials evaluated the addition of anti-PD-1 ICI to BRAF/MEK inhibitor combination in *BRAF* mutant melanoma and reported higher PFS and greater durations of response with combined immunotherapy and targeted therapy, although notably the toxicity of the triplet regimens was considerable (120-123). Two separate phase III trials reported modest improvements in PFS with combined immunotherapy and targeted therapy compared with targeted therapy alone, and while this was statistically significant in IMspire150 (124), it was not in COMBI-I (125), and overall has not resulted in widespread adoption of the atezolizumab vemurafenib/cobimetinib triplet despite regulatory approval. However, untreated MBM patients were excluded from the studies, and the evidence for efficacy in active MBM is limited.

The combination of ipilimumab and vemurafenib was tested in a small phase II study in advanced melanoma, 6 of whom had MBM (126). Sequential administration of vemurafenib and ipilimumab led to disease control in 7 patients (5 patients with partial response and 2 with stable disease). The median PFS was 8 months, which was an improvement compared to the PFS seen with either drug, however, the combination was particularly toxic leading to discontinuation.

NIBIT-M1 was a phase II study which evaluated the efficacy of ipilimumab in combination with fotemustine, a chemotherapeutic agent with known CNS penetrance (127,128). This combination was based on the hypothesis that fotemustine would generate TA and consequently TA-specific T cells, a response that could be amplified by ipilimumab. 86 patients with advanced melanoma were enrolled, 20 out of which had brain disease. The intra-cranial RR was 50%, with 25% patients achieving partial response or stable CNS disease, and 25% without detectable disease on scans. Median OS in patients with brain disease was 12.7 months and 2- and 3-year survival rates were 38.9% and 27.8% respectively. Median PFS was 3.4 months in this subset of patients. NIBIT-M2 is an ongoing phase III study (*Table 3*) which plans to enroll 168 patients with MBM wherein fotemustine with or without ipilimumab will be evaluated against the combination of ipilimumab/nivolumab.

Combined local and systemic therapy

Despite the encouraging results seen in the clinical trials, a significant proportion of MBM patients are either resistant to systemic treatment or acquire resistance to systemic treatment over time (129). One of the treatment strategies to overcome this obstacle is combining local (neurosurgery

vs. radiosurgery) and systemic therapies. Pooled analyses of various studies have shown improved 1-year survival and improved regional control in patients who receive SRS and ICI concurrently compared to SRS alone (130). When it comes to the synergistic effect seen between BRAF inhibitors and SRS, the radiosensitizing effect of this drug class on melanoma cells plays an important role. This effect, originally seen in preclinical studies (131), has been validated in the clinical setting by pooled analyses which have shown a significant survival advantage with the combination of BRAFi and SRS compared to SRS alone (132). Combination therapy, however, carries the potential for increased toxicities such as the increased risk of radiation necrosis with ICI/SRS combination (133) and intracranial hemorrhage with BRAF inhibitor/SRS combination (132). More data from other retrospective and prospective studies is needed to further characterize adverse events from combined local and systemic therapy (*Table 4*).

Adoptive cellular therapy (ACT) in MBM

ACT is demonstrably effective in highly refractory melanoma with ORR 36–41% (134,135). Despite early reports of efficacy in MBM (136), the evaluation of ACT in MBM has been unexpectedly slow due to the ACT-specific limitations, in particular the complexity entailed in generation and administration of autologous TIL which has restricted this therapy to specialized centers with expertise in this area.

A phase II study of ACT from NIH that included MBM reported intracranial responses in 5 out of 15 patients with previously treated CNS disease and 6 out of 18 patients with previously untreated CNS disease (137). Of note, the PFS was significantly less in patients with CNS disease compared to patients without CNS disease. In a small, randomized phase II study of ACT with or without antigen-loaded dendritic cells (DC) in a mostly ICI-naïve melanoma patient population, a small fraction of patients had durable responses including patients with untreated MBM. Pooled analyses have showed a significant response rate (32–38%) in patients who received TIL as a second line therapy after ICI failure. However, emerging data is showing poorer response in patients who receive TIL after ICI failure compared to ICI-naïve patients (134).

Sustained response after ACT is dependent on various factors, including higher doses of TIL (≥50 billion), higher absolute number of $CD8^+$ cells in transfused cells, "young" TIL, high dose IL-2 and the *in vitro* conditions during expansion and priming of T-cells which affect T-cell functionality and longevity (134,138). These *in vitro* conditions are a focus of ongoing research and include potassium concentration (134,139), intracellular concentrations of L-arginine (140), rate of T-cell metabolic activity during *in vitro* expansion and priming (141), and cholesterol metabolism in T-cells (142). Transduction of T-cells with chimeric antigen receptors (CAR-T) and TCR gene modified T cells are other forms of adoptive cell therapies that are currently under investigation. The one-off nature of ACT and its tolerable toxicities compared to other systemic therapies makes it ACT a promising mode of therapy for MBM, although improving the survival of transduced T cells remains an ongoing challenge. The use of novel IL-2 pathway agonists, and other cytokines such as IL-7, IL-15, IL-18 to expand TIL *ex vivo* is promising, although it remains unclear if these data can be translated into the MBM setting.

Special circumstances

Leptomeningeal disease

Melanoma LMD carries a dismal prognosis, with median survival being only a few weeks (6), and limited data regarding effective treatment options. While RT may be considered for symptomatic areas of the spine (143), there is a paucity of evidence regarding the role of systemic therapy in LMD. Case reports and series support efficacy of BRAF/MEK inhibitors in *BRAF* mutated LMD (144-146). In Cohort C of the ABC trial, 4 out of 16 patients had LMD and were treated with single-agent nivolumab, with no intracranial responses being observed (88). Intrathecal (IT) interleukin-2 (IL-2) has been used in a small study of LMD patients with models results (median OS 7.8 months, 1-, 2-, and 5-year OS rates of 36%, 26%, and 13%, respectively) (147). The study also showed an improvement in radiological findings on brain imaging in 39% patients, and in 32% patients on spine imaging. The role of combined IT and systemic anti-PD-1 is being evaluated in a phase I/II study in LMD (NCT03025256).

Future directions

Multiple studies have been developed to improve upon prior results, and are summarized in *Table 4*. These include systemic ICIs in combination with agents such as VEGF inhibitors lenvatinib (KEYMAKER-U02D,

Table 4 Ongoing studies of targeted therapies and immune checkpoint inhibitors in MBM patients

Study (title/reference); phase	Trial identifier	Sample size	Target population	Intervention	Pertinent study endpoints
Pembrolizumab Plus Bevacizumab for Treatment of Brain Metastases in Metastatic Melanoma or Non-small Cell Lung Cancer; Phase II	NCT02681549	53 (40 melanoma patients)	Asymptomatic, lesions 5–20 mm in size, no high-dose (≤10 mg prednisone or equivalent) steroid use	Systemic pembrolizumab + bevacizumab	Primary: brain metastases response rate. Secondary: PFS in the brain or the body; safety and toxicity of combination pembrolizumab and bevacizumab
PD-L1 Therapy Combined With Anti-VEGF Therapy in Unresectable or Metastatic Melanoma; Phase II	NCT04356729	30	Asymptomatic, not on corticosteroids	Atezolizumab + bevacizumab	Primary: Overall RR. Secondary: OS, time to progression, DOR, incidence of AE
Low Dose Ipilimumab With Pembrolizumab in Treating Patients With Melanoma That Has Spread to the Brain; Phase II	NCT03873818	30	Asymptomatic, lesions 5–30 mm in size, no prior local treatment	Systemic pembrolizumab and low-dose ipilimumab 1 mg/kg	Primary: CBR. Secondary: OS; PFS; incidence of AEs and SAEs
Pembrolizumab and Lenvatinib in Patients With Brain Metastases From Melanoma or Renal Cell Carcinoma; Phase II	NCT04955743	56	Asymptomatic, lesions 5–30 mm in size, no prior local treatment	Pembrolizumab + Lenvatinib	Primary: best brain metastasis RR. Secondary: best overall objective RR; PFS; OS; brain metastasis DOR
Substudy 02D: Safety and Efficacy of Pembrolizumab in Combination With Investigational Agents or Pembrolizumab Alone in Participants With Melanoma Brain Metastasis (MK-3475-02D/KEYMAKER-U02); Phase I/II	NCT04700072	300	Asymptomatic; no systemic steroids	Coformulation pembrolizumab/ quavonlimab + Lenvatinib *vs.* pembrolizumab + lenvatinib	Primary: % patients with AEs; % patients who discontinue study due to AEs; objective response rate. Secondary: DOR; brain metastasis response rate; brain metastasis DOR; PFS
Troriluzole or Placebo Plus Ipi Plus Nivo in Mel Brain Mets; Phase II	NCT04899921	103	Asymptomatic, lesions 5–30 mm in size, no prior local therapy or WBRT, not on steroids, must have prior anti-PD-1 therapy	Ipilimumab + nivolumab +/– troriluzole	Primary: PSF. Secondary: OS; intracranial RR; intracranial PFS; extracranial RR; extracranial PFS; treatment related AEs; treatment tolerability; corticosteroid usage; frequency of SRS and surgical intervention to brain
Study Comparing Investigational Drug HBI-8000 Combined With Nivolumab *vs.* Nivolumab in Patients With Advanced Melanoma; Phase III	NCT04674683	480	No prior ICI use, no steroid use	Nivolumab +/– HBI-8000	Primary: objective RR; PFS. Secondary: OS; safety; DOR; disease control rate
A Study of Fotemustine (FTM) *vs.* FTM and Ipilimumab (IPI) or IPI and Nivolumab in Melanoma Brain Metastasis (NIBIT-M2); Phase III	NCT02460068	168	Asymptomatic, lesions 5 to 20 mm in size, no prior therapy for advanced disease	Fotemustine +/– ipilimumab *vs.* ipilimumab/nivolumab	Primary: OS. Secondary: safety; intracranial and extracranial disease control rate; PFS; ORR; TTR; DOR; brain-PFS
E6201 Plus Dabrafenib for the Treatment of Metastatic Melanoma Central Nervous System Metastases; Phase I	NCT03332589	24	Symptomatic *vs.* asymptomatic, lesion 5 to 30 mm in size	E6201 + dabrafenib	Primary: intracranial ORR. Secondary: intracranial disease duration of response; systemic disease overall response rate; PFS; OS; safety of E6201
Bevacizumab and Atezolizumab With or Without Cobimetinib in Treating Patients With Untreated Melanoma Brain Metastases (TACo-BEAT-MBM); Phase II	NCT03175432	60	Asymptomatic or mildly symptomatic, lesion 5–30 mm in size	Systemic atezolizumab and bevacizumab +/– Cobimetinib	Primary: objective intracranial response rate (OIRR); safety, tolerability, and efficacy of atezolizumab, bevacizumab, and cobimetinib. Secondary: incidence of adverse events; ORR (intracranial + extracranial); DOR; PFS; OS
A Study to Compare the Administration of Encorafenib + Binimetinib + Nivolumab Versus Ipilimumab + Nivolumab in BRAF-V600 Mutant Melanoma With Brain Metastases; Phase II	NCT04511013	112	Lesions ≥5 mm in size, no steroids higher than 8 mg daily dexamethasone, no prior systemic therapy for metastatic disease	Binimetinib + encorafenib + nivolumab *vs.* ipilimumab + nivolumab	Primary: PFS. Secondary: OS; intracranial RR; objective RR; DOR
Melanoma Metastasized to the Brain and Steroids (MEMBRAINS); Phase II	NCT03563729	80	Need for systemic steroids	Arm B: pembrolizumab Arm C: ipilimumab + nivolumab Arm D: ipilimumab + nivolumab Arm E: BRAF/MEK inhibitor → ipilimumab/nivolumab	Primary: 6-month PFS; 6-month OS. Secondary: overall PFS; OS; ORR; extracranial RR; intracranial RR; intracranial CBR
Safety and Efficacy in Participants With Metastatic BRAF-mutant Melanoma Treated With Encorafenib With and Without Binimetinib in Combination With Nivolumab and Low-dose Ipilimumab (QUAD01); Phase I/II	NCT04655157	84	Symptomatic *vs.* asymptomatic; steroids less than 4 mg daily dexamethasone or equivalent	Cohort 1: encorafenib + nivolumab/ipilimumab Cohort 2: encorafenib/ binimetinib + nivolumab/ ipilimumab	Primary: Phase II doses of both combinations. Secondary: RR; CBR; AEs; PFS
A Study Evaluating the Safety and Efficacy of Cobimetinib Plus Atezolizumab in BRAFV600 Wild-type Melanoma With Central Nervous System Metastases and Cobimetinib Plus Atezolizumab and Vemurafenib in BRAFV600 Mutation-positive Melanoma With Central Nervous System Metastases (MO39136); Phase II	NCT03625141	80	No prior WBRT	Cohort 1: cobimetinib + atezolizumab Cohort 2: cobimetinib/ vemurafenib + atezolizumab	Primary: Intracranial ORR. Secondary: Extracranial ORR; Overall ORR; PFS; DOR; DCR; OS; Occurrence and severity of AEs

Table 4 (*continued*)

Table 4 (*continued*)

Study (title/reference); phase	Trial identifier	Sample size	Target population	Intervention	Pertinent study endpoints
Vemurafenib and Cobimetinib Combination in BRAF Mutated Melanoma With Brain Metastasis (CONVERCE); Phase II	NCT02537600	43	Cohort A: asymptomatic, no prior local treatment Cohort B: asymptomatic, prior local treatment Cohort C: symptomatic, with or without prior local treatment Lesions 5–40 mm in size	Vemurafenib + cobimetinib	Primary: intracranial RR in cohort A. Secondary: intracranial RR in cohorts B, C; intracranial DOR, overall DOR, ORR, OS, frequency of AEs, PFS
Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients With BRAFV600-mutant Melanoma Brain Metastasis (POLARIS); Phase II	NCT03911869	13	Asymptomatic, lesions 5–40 mm in size Cohort 1: can have prior local treatment Cohort 2: no prior local treatment	Cohort 1: Binimetinib + standard dose encorafenib Cohort 2: Binimetinib + high dose encorafenib	Primary: intracranial RR. Secondary: extracranial RR, global RR, DCR, DOR, PFS, OS, incidence of AEs
A FIH Study of PF-07284890 in Participants With BRAF V600 Mutant Solid Tumors With and Without Brain Involvement; Phase I	NCT04543188	225	Part B Cohort 1: asymptomatic, no prior BRAFi or MEKi Cohort 2: symptomatic, no prior no prior BRAFi or MEKi Cohort 3: asymptomatic, prior BRAFi use Cohort 4: symptomatic, prior BRAFi use Cohort 5: LMD +/– brain disease, symptomatic *vs.* asymptomatic	Part A: ARRY-461 +/– binimetinib Part B: ARRY-461 + binimetinib	Primary: overall RR. Secondary: treatment related AEs, PFS, DCR, OS, DOR, TTR
Pembrolizumab and Stereotactic Radiosurgery for Melanoma or Non-Small Cell Lung Cancer Brain Metastases; Phase I	NCT02858869	30	Asymptomatic, 1–10 untreated lesions, largest lesions <14.15 cc^3	Pembrolizumab + SRS	Primary: dose limiting toxicity. Secondary: ORR; OS; rate of distant brain failure; rate of LMD; rate of local recurrence; rate of symptomatic RN
Combining Radiosurgery and Nivolumab in the Treatment of Brain Metastases; Phase II	NCT02978404	26	No prior local treatment	Nivolumab + SRS	Primary: Intracranial PFS. Secondary: Treated brain lesion control rate; OS; maximum response rate of distant non-irradiated disease; PFS; correlation between PD-L1 expression and clinical outcomes; neurocognitive function; acute and late toxicity
SRS and Nivolumab in Treating Patients With Newly Diagnosed Melanoma Metastases in the Brain or Spine; Phase I	NCT02716948	17	Asymptomatic, untreated lesions, ≥3 mm in size	Nivolumab + SRS	Primary: incidence of SAE. Secondary: incidence of toxicity; local DCR; PFS; systematic DCR
Anti-PD 1 Brain Collaboration + Radiotherapy Extension (ABC-X Study); Phase II	NCT03340129	218	Asymptomatic, lesions 5–40 mm in size, No prior local or systemic treatment for BM	Ipilimumab + nivolumab +/– SRS	Primary: neurological specific cause of death. Secondary: intracranial and extracranial RR; ORR; overall PFS; non-neurological specific cause of death; OS; incidence of RN; requirement of salvage radiotherapy or intracranial surgery; change in neurocognitive function scores; time to and duration of neurological deterioration; PS; AEs
Encorafenib and Binimetinib Before Local Treatment in Patients With BRAF Mutant Melanoma Metastatic to the Brain (EBRAIN-MEL); Phase II	NCT03898908	38	Asymptomatic *vs.* symptomatic, no prior local therapy	Neoadjuvant encorafenib/ binimetinib prior to local therapy	Primary: intracranial objective response (iORR) in Cohort 1 (asymptomatic patients, N=48). Secondary: iORR in Cohort 2 (symptomatic patients, N=15); global intracranial response; duration of intracranial response; duration of global response; intracranial PFS; global PFS; % patients free of progression; OS; % patients alive; number of subjects with treatment-related AEs until and after local treatment; change in QoL
Vemurafenib Plus Cobimetinib After Radiosurgery in Patients With BRAF-mutant Melanoma Brain Metastases (RadioCoBRIM); Phase II	NCT03430947	20	Symptomatic, lesions 5–40 mm in size, <10 lesions	Adjuvant vemurafenib + cobimetinib after radiosurgery	Primary: intracranial ORR. Secondary: extracranial ORR; ORR for whole-body tumor sites; intracranial DOR; extracranial DOR; PFS; OS; incidence of adverse events
Concurrent Dabrafenib + Trametinib With Sterotactic Radiation in BRAF Mutation-Positive Malignant Melanoma and Brain Metastases; Phase II	NCT02974803	6	Lesions 10–40 mm in size, 1–10 lesions	Dabrafenib + trametinib + SRS	Primary: intracranial RR. Secondary: extracranial RR, DOR, intracranial PFS, overall PFS, overall RR
Binimetinib Encorafenib Pembrolizumab +/– SRS in BRAFV600 Melanoma With Brain Metastasis (BEPCOME-MB); Phase II	NCT04074096	150	Asymptomatic, lesions 5–30 mm in size, <10 lesions	Encorafenib + binimetinib + pembrolizumab +/– upfront SRS	Primary: intracranial PFS. Secondary: Intracranial RR; intracranial DC; extracranial RR; ORR; duration of intracranial, extracranial and overall response; duration of response of treated targeted lesions; PFS; OS; cognitive performance; AEs
Optune Device - TT Field Plus Nivolumab and Ipilimumab for Melanoma with Brain Metastasis; Phase II	NCT03903640	23	Lesions >10 mm, no prior WBRT, steroids less than 4 mg daily dexamethasone or equivalent	Ipilimumab + nivolumab + Optune device	Primary: intracranial PFS. Secondary: OS; best intracranial RR; beat extracranial RR; extracranial PFS; safety of treatment regimen
Safety and Efficacy of Sonocloud Device Combined with Nivolumab in Brain Metastases From Patients with Melanoma (SONIMEL01); Phase I/II	NCT04021420	21	Lesions 5–35 mm in size, no prior local therapy, no prior anti-PD1 therapy	SonoCloud + nivolumab	Primary: most successful dose. Secondary: best ORR; ORR; best intracranial ORR; intracranial ORR; best extracranial ORR; extracranial ORR
NovoTTF-200A + Pembrolizumab In Melanoma Brain Metastasis; Phase I/II	NCT04129515	30	Lesions 10–30 mm in size; 4mg daily or higher dexamethasone use	Systemic pembrolizumab + NovoTTF-200A	Primary: number of participants with dose limiting toxicity. Secondary: ORR; 6-month PFS; QoL assessment
STAT3 Inhibitor WP1066 in Treating Patients With Recurrent Malignant Glioma or Progressive Metastatic Melanoma in the Brain; Phase I	NCT01904123	8	Progression on or tolerance to standard of care therapies, Lesions ≥10 mm in size	STAT3 Inhibitor WP1066	Primary: maximum tolerated dose, incidence of AEs. Secondary: RR, DOR, OS, PFS, % patients with additional metastatic lesions

MBM, melanoma brain metastases; PFS, progression free survival; RR, response rate; OS, overall survival; DOR, duration of response; AEs, adverse events; CBR, clinical benefit rate; SAE, serious adverse event; WBRT, whole-brain radiation therapy; DCR, disease control rate; LMD, leptomeningeal disease; ORR, overall response rate; PS, performance status; QoL, quality of life; RN, radiation necrosis; stereotactic SRS, radiosurgery; TTR, time to response.

NCT04700072) and bevacizumab (NCT04356729), novel glutamate modulator troriluzole (NCT04899921), and tumor treating fields (TTF) devices such as NovoTTF-100A (NCT04129515) or Sonocloud (SONIMEL01, NCT04021420).

Beyond the systemic administration of ICIs, IT approaches using various immunotherapies are currently being investigated in melanoma. IT IL-2 was first assessed in patients with melanoma patients with LMD. While response rates were low and the associated toxicities significant, a subset of melanoma patients with LMD treated with IT IL-2 achieved durable long-term survival with 1-, 2- and 5-year OS rates of 36%, 26%, and 13% (147). An ongoing study (NCT03025256) is evaluating combined systemic and IT nivolumab in this patient population.

As noted earlier, compelling data suggests synergies between PD-1 or CTLA-4 targeting ICIs and RT for the treatment of MBM, supported by data from retrospective series (148). These have led to a plethora of studies evaluating SRS combined with either single agent anti-PD-1 (NCT02716948, NCT02978404, and NCT02858869) or PD-1/CTLA-4 doublet (NCT03340129) in MBM.

Other studies are evaluating novel small molecules including the class I selective oral HDAC inhibitor HBI-8000 (NCT04674683) and STAT3 inhibitor WP1066 (NCT01904123).

Conclusions

Despite the recent advances in the understanding of molecular and genetic etiopathogenesis of advanced melanoma and development of effective treatments, MBM remains a challenging disease and thorny management problem underscored by poor prognosis of MBM patients in multiple real-world reports (149-152). ICI and targeted therapy have both led to significant improvements in the intracranial disease control. However, both treatment modalities carry the inherent risk of development of resistance and loss of response. The combination of ICI and targeted therapy has also been evaluated in a small number of clinical trials and has shown modest improvement in outcomes compared to either therapy alone. However, clinical trial data has also shown a significant amplification of toxicities with combination therapy which has led to limited adoption of this treatment model. Despite the current advances and the success of currently available therapies, sub-populations such as LMD and patients with progressive disease remain an extremely challenging population with relatively limited treatment options and poor outcomes. Novel treatments such as ACT have shown favorable outcomes in the heavily pre-treated population and remains an option for salvage treatment, despite the limitations associated with production and administration of engineered T-cells. MBM continues to be an area of immense research interest and multiple clinical trials are underway to evaluate combinations of various systemic agents, combined systemic and local therapy, and systemic agents and implantable devices. Further data is awaited to determine the most favorable combination of systemic and local therapies that can maximize the depth and length of response with minimum toxicities.

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