Current and Emerging Options for Patients With Melanoma Brain Metastases

Firas Y. Kreidieh, MD, and Hussein A. Tawbi, MD, PhD

Department of Melanoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding author:
Hussein Tawbi, MD, PhD
Department of Melanoma Medical Oncology
Division of Cancer Medicine
The University of Texas
MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, TX 77030
Email: HTawbi@mdanderson.org
Tel: (713) 792-6161

Abstract: Melanoma is the most aggressive skin cancer, with a high incidence of metastatic spread and a predilection for metastases to the brain. It represents the third most common origin of brain metastases after breast and lung cancer. With the advent of targeted therapy and immunotherapy in melanoma, along with improved local therapy options such as stereotactic radiosurgery (SRS), the treatment of melanoma brain metastases (MBM) has led to significant improvements in outcome. In this review, we provide an overview of management options for patients with MBM while highlighting emerging treatment options. Surgery may be considered for patients with symptomatic MBM, whereas SRS is considered standard for patients with 1 to 4 brain lesions. Combination immunotherapy has led to durable intracranial responses and improved long-term outcomes for patients with asymptomatic MBM. The data available to date have shown that patients with MBM can have a durable response and overall response that are similar to those of patients without brain metastases, and additional trials are ongoing. Mounting evidence suggests that patients with MBM should be considered for inclusion in clinical trials, which range from early-phase trials to phase 3 studies, to accelerate much-needed drug development in this population.

Keywords
Checkpoint inhibitor, ipilimumab, melanoma, nivolumab, symptomatic brain metastases

Introduction

Melanoma is an aggressive skin cancer that will account for an estimated 99,780 new diagnoses in 2022 in the United States; the age-standardized incidence rate recently reached 22.7 per 100,000.[1] Melanoma has one of the highest tendencies to metastasize to the brain among primary solid malignancies in adults, and is the third most common origin of brain metastases after breast and lung cancer.[2,3] Estimates suggest that more than one-third of patients with stage IV melanoma have brain metastases at the time of diagnosis, and up to 75% of patients with advanced melanoma have brain metastases at the time of death.[2,4] The presence of melanoma brain metastases (MBM) has been associated with significant neurologic

morbidity and disease-related mortality. The historical prognosis for patients with MBM was generally dismal, with a median overall survival (OS) that rarely exceeded 6 months.[2,5]

Until recently, the management of MBM has primarily relied on local therapy, namely surgery and/or radiation therapy. A deeper understanding of the biology of melanoma and its interactions with the immune system over the past decade has significantly revolutionized the therapeutic options for patients with metastatic disease. In addition, with the advent of immunotherapy in melanoma and improved local therapy options such as stereotactic radiosurgery (SRS), we have seen a significant improvement in outcome in patients with MBM, with the median OS exceeding 2 years.[6,7] In this review, we provide an overview of management options for patients with MBM and highlight the new treatment options on the horizon.

Surgery

Surgical resection is considered as a primary approach to MBM in 2 circumstances when the tumor is surgically accessible: if the condition involves a solitary brain lesion or if the lesions are symptomatic owing to vasogenic edema and/or mass effect.[8] In addition to providing disease control, surgical resection of MBM enables oncologists to obtain a tissue sample for diagnostic and molecular testing. Obtaining this tissue sample is particularly important in patients whose first presentation includes brain metastases, either in the absence of a tissue diagnosis or in the absence of extracranial disease. Also, reports have indicated a potential change in the molecular profile from the primary site to the metastatic disease in the brain following a branched evolution model that could affect the choice of molecularly targeted therapy.[9] Fife and colleagues analyzed data from 1137 patients with MBM in Australia and reported that surgical resection was associated with significantly improved survival (P<.0001).[10] Wasif and colleagues studied the survival benefit of metastectomy in 4229 patients with MBM. Metastectomy was associated with an improved OS, with a 5-year OS of 16% among those who underwent the procedure compared with 7% for those who did not undergo the procedure (P<.001).[11] Alvarez-Breckenridge and colleagues showed that upfront surgical resection of MBM can be associated with a therapeutic advantage when performed before initiation of immunotherapy. Surgical resection followed by immunotherapy was associated with a median OS of 22.7 months, as compared with 10.8 and 9.4 months for patients who were treated with immunotherapy alone and immunotherapy followed by surgery, respectively.[12]

Although these series data have shown a survival benefit for surgical resection in patients with MBM, there remains a scarcity of prospective data. Also, there are no evidence-based guidelines regarding the number of brain lesions that can be safely resected, but rather consensus recommendations that integrate the patient's safety and clinical scenarios. Gazzeri and colleagues analyzed 57 patients who underwent surgical resection of brain metastases, 35 of whom had multiple brain lesions. The authors reported that surgical management for multiple metastatic brain lesions was associated with an improved quality of life and longer OS.[13] In general, patients are considered suitable for metastectomy if they have a Karnofsky performance status of 970 or greater, controlled extracranial disease status, surgically accessible brain lesions, and up to 3 to 4 brain lesions.[2,13,14]

Decision-making regarding surgical resection requires careful patient selection in order to maximize the potential benefit. The decision is usually driven by metastases-associated symptoms, along with the size, location, and characteristics of the metastases. Although resection of multiple lesions has been demonstrated to be technically feasible, it does require vastly experienced neurosurgeons and multiple craniotomies. It is therefore most common for surgery to be reserved for single, relatively large lesions that are causing debilitating symptoms or are rapidly progressive. Surgery is deferred in favor of radiation or systemic therapy in certain circumstances. An important consideration is that these circumstances may also render patients ineligible for enrollment in clinical trials, an exclusion that can confound the interpretation of results. As we detail later in this review, clinical trials of systemic therapy generally have not included patients with symptomatic brain metastases, and local therapies with surgery or radiation are typically prioritized for this population. In addition, patients with MBM are considered a challenging population with unique characteristics (eg, comorbidities, risk of thromboembolic events) that should be taken into consideration when making such decisions.[15,16] Surgical resection also may delay the initiation of systemic therapy and/or radiation therapy in order to maintain proper wound healing following surgery.

Whole-Brain Radiation Therapy

Whole-brain radiation therapy (WBRT) is a traditional approach to MBM that has limited efficacy and is normally reserved for patients with numerous symptomatic brain metastases or symptomatic leptomeningeal carcinomatosis. Although WBRT theoretically can address both macroscopic and microscopic disease in the brain, the median OS associated with this approach remains poor, and neurotoxicity remains a concern.[2,4] To date, there are no randomized controlled trials that compare WBRT

with other modalities. Results from the QUARTZ study by Mulvenna and colleagues showed that WBRT did not provide additional clinically significant benefit to patients with non–small cell lung cancer with brain metastases.[17] As such, the expected benefit of WBRT in MBM likely would not be high, especially given that melanoma cells are particularly resistant to radiotherapy owing to their DNA repair ability.[4] In fact, in patients who receive WBRT, the reported median OS was only 2 to 5 months and the 1-year OS was less than 12%.[2,17-19] The limited reported benefit of WBRT indicates that patient selection is important when considering this option. WBRT may be considered in patients with more than 4 metastatic brain lesions and in those for whom SRS may be difficult, as discussed in the following section. In addition, WBRT may be considered in patients who have leptomeningeal disease or are at high risk for it.[20]

The most commonly used WBRT regimens are 30 Gy given in 10 fractions or 20 Gy given in 5 fractions in a daily dosing schedule.[2] Toxicity from WBRT includes cognitive dysfunction associated with impaired memory and reduced performance status.[2,4] Interventions that can minimize neurotoxicity include conformal avoidance intensity-modulated radiation therapy that spares the hippocampus and the use of the N-methyl-D-aspartate (NMDA) receptor antagonist memantine hydrochloride, which binds to NMDA receptors in the cortex and hippocampus.[4,21,22] The RTOG 0614 trial demonstrated less cognitive impairment among patients who received memantine hydrochloride during and after WBRT, compared with patients who received WBRT alone.[21] RTOG 0933 was a phase 2, multi-institutional single-arm trial that compared hippocampus conformal avoidance WBRT for brain metastases vs historical controls of patients treated with WBRT without hippocampus avoidance. Hippocampus avoidance was associated with better preservation of cognitive function and quality of life.[22,23] Moreover, preclinical studies have shown an association between modest radiation therapy doses and a decrease in neurogenesis at the level of the hippocampus subgranular zone, which is responsible for new memory formation.[24]

Stereotactic Radiosurgery

The development of precision radiation oncology and high-resolution MRI over the past 2 decades has made it possible to treat 1 or more metastatic brain lesions with a concentrated high dose of radiation while avoiding surrounding normal brain tissue.[2,4] This development is of particular significance because melanoma tends to be radioresistant.[2,25] SRS is currently recommended over WBRT for MBM with up to 4 brain lesions. Ongoing clinical trials are studying the efficacy of SRS for patients with at least 5 MBM brain lesions.[26-28] Local control rates in patients with MBM who receive SRS have been reported to reach 90%, with a 1-year survival rate of 25%.[29,30] Although no large randomized trials have compared SRS with surgical resection, a few small randomized trials and retrospective studies have suggested that the efficacy of SRS is equal to that of surgical resection.[31,32]

Despite its excellent local control in MBM, the majority of data could not show benefit in OS after SRS.[33,34] Moreover, data from retrospective analyses and a few randomized trials did not show a survival benefit from combining SRS with WBRT.[33-35] The Alliance trial randomly assigned 213 patients with 1 to 3 brain metastases to receive SRS alone (n=111) or SRS plus WBRT (n=102). Brown and colleagues demonstrated a lower cognitive decline in the SRS group than in the SRS/WBRT group (63.5% vs 25%, respectively) in this trial, along with a better quality of life in the SRS group.[36] As such, SRS plus regular surveillance by imaging is used rather than SRS/WBRT for patients with MBM with brain lesions that are no larger than 3 cm in size and are limited in number.[2,33]

Targeted Therapy

Although targeted therapy has significantly improved the management of metastatic melanoma, patients with MBM generally have been excluded from the majority of clinical trials that served as the basis for approval of targeted therapeutic drugs. Subsequent single-arm phase 2 studies did investigate the intracranial activity of BRAF-targeted therapy.[37] The BREAK-MB trial was a multicenter, open-label phase 2 trial that enrolled 172 patients, from 24 centers in 6 countries, with *BRAF* V600–mutated MBM to study the efficacy and safety of dabrafenib (Tafinlar, Novartis). Patients were divided into 2 cohorts: cohort A (n=89) included patients who did not receive prior local therapy to brain metastases and cohort B (n=83) included patients whose brain metastases progressed after prior local therapy to the brain. The intracranial response rate was 39.2% in cohort A and 30.8% in cohort B. In patients who harbored a *BRAF* V600K mutation, the intracranial response rate was 6.7% in cohort A and 22.2% in cohort B. This study demonstrated the efficacy and acceptable safety profile of dabrafenib in patients with *BRAF*-mutated MBM regardless of whether they had not received prior treatment to the brain or had been treated for brain metastases and experienced progression.[38]

Another study by McArthur and colleagues investigated the safety and efficacy of vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) in patients with *BRAF* V600–mutated MBM.[39] This phase 2 study enrolled 146

patients who were divided into 2 cohorts, similar to the BREAK-MB study: cohort 1 (n=90) included patients who did not receive prior local therapy to brain metastases and cohort 2 (n=56) included patients whose brain metastases progressed after prior local therapy to the brain. The intracranial response rate was 18% in both cohorts, and the intracranial disease control rate was similar, at 61% in cohort 1 and 59% in cohort 2. The median progression-free survival (PFS) was similar in both cohorts, at 3.7 months and 4 months, respectively. The median OS was similar in both cohorts, at 8.9 months and 9.6 months, respectively. This study further supported the efficacy of BRAF inhibitors in *BRAF*-mutated MBM.

In addition to prospective trials on BRAF inhibitors, other trials combined BRAF inhibitors with MEK inhibitors in *BRAF*-mutated MBM. Davies and colleagues conducted an open-label phase 2 trial of a combination of dabrafenib and trametinib (Mekinist, Novartis) called the COMBI-MB trial.[40] This study enrolled 125 patients with *BRAF* V600–mutated MBM, who were divided into 4 groups. Cohort A included 76 patients who harbored a *BRAF* V600E mutation and had asymptomatic brain metastases with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and cohort B included 16 patients who had similar features as cohort A but had received prior local therapy to the brain. Cohort C included 16 patients who harbored a *BRAF* V600D/K/R mutation and asymptomatic brain metastases with or without prior brain therapy and an ECOG status of 0 or 1, and cohort D included 17 patients who harbored a *BRAF* V600D/K/R mutation and had symptomatic brain metastases with or without prior brain therapy and an ECOG status of 0, 1, or 2. Patients with leptomeningeal disease and brain lesions larger than 4 cm in diameter were excluded. The intracranial response rate was 58%, 56%, 44%, and 59% for cohorts A, B, C, and D, respectively.[40] This trial, therefore, demonstrated improved intracranial response in *BRAF* V600–mutated MBM with a combination of dabrafenib and trametinib.[40] However, despite the favorable intracranial response rates reported in the COMBI-MB trial, the study showed a modest median duration of control of brain metastases of 6.5 months.[40]

Retrospective data on single-agent BRAF inhibitors, namely dabrafenib and vemurafenib, showed an intracranial response ranging from 42% to 50% and an intracranial disease control rate of up to 83%. The median PFS and OS were up to 5.5 months and 9.5 months, respectively.[41-45] Combining BRAF inhibitors with MEK inhibitors, such as dabrafenib plus trametinib, vemurafenib plus cobimetinib (Cotellic, Genentech), or encorafenib (Braftovi, Pfizer) plus binimetinib (Mektovi, Pfizer), was associated with an intracranial response rate of up to 43%, an intracranial disease control rate of up to 79%, a median PFS of 5.8 months, and a median OS of 11.2 months.[46,47] A case series by Holbrook and colleagues included 24 patients with metastatic *BRAF*-mutated MBM who were treated with encorafenib and binimetinib in 3 centers in the United States.[48] This combination therapy was associated with an intracranial response rate of 24%, a median duration of response of 22 weeks, and a clinical benefit rate of 57%. It is worth noting that 88% of the patients had been treated previously with BRAF/MEK inhibitors, which suggests the possibility of re-challenging metastatic *BRAF*-mutated MBM with these agents.[48,49]

The possibility of re-challenging with BRAF/MEK inhibitors was further supported by data from a systematic review by Viñal and colleagues that showed an objective response rate (ORR) of up to 43% and a disease control rate reaching 72%.[50] Three-quarters of the patients in this study who had a partial response had a history of brain metastases, but the review does not indicate the intracranial response rate of patients with MBM. A retrospective study by Valpione and colleagues analyzed 116 patients with metastatic melanoma who received prior BRAF inhibition and who were re-challenged with BRAF/MEK inhibitors. Brain metastases were present in 44% of patients at the time of re-challenge. The median OS was 9.8 months and the median PFS was 5 months.[51] These data do not specifically indicate the intracranial response rate for patients with MBM. Results from Holbrook and colleagues, combined with the favorable retrospective data on patients who were re-challenged with BRAF/MEK inhibition, suggest this as a possible treatment approach even in patients who have received prior targeted therapy.[50,51]

There remains a scarcity of data on patients whose disease progresses extracranially during treatment with BRAF/MEK inhibitors. Cagney and colleagues reported a cases series of patients who had rapid progression of brain metastases after discontinuation of dabrafenib/trametinib owing to extracranial disease progression or toxicity. As such, close surveillance shortly following cessation of BRAF/MEK inhibitors is recommended to detect possible brain disease progression early on.[52]

Immunotherapy

The initial role of immunotherapy in MBM dates back to 2 case reports published in 2008 and 2010 that showed response of MBM to the anti–cytotoxic T-lymphocyte–associated antigen 4 (anti–CTLA-4) agent ipilimumab (Yervoy, Bristol Myers Squibb).[53,54] These case reports were followed by a series of clinical trials that investigated the role of immunotherapy in MBM. A phase 2 study by Margolin and colleagues in 2012 included 72 patients divided into 2 cohorts: patients with no neu-

rologic symptoms and not receiving corticosteroids and patients with neurologic symptoms and on a stable dose of corticosteroids. Both cohorts received ipilimumab, which showed an ORR, PFS, and OS that were similar to those of patients without brain metastases. The benefit was particularly pronounced for patients who did not have neurologic symptoms and whose brain tumors were small.[55,] The study showed a worse outcome in patients who required corticosteroids, which the investigators attributed to the different prognoses of the included patients within each cohort and to the possible negative effect of corticosteroids on immunotherapy.[34,55]

In an attempt to enhance the efficacy of ipilimumab in MBM, the Italian phase 2 NIBIT-M1 trial combined ipilimumab with fotemustine, a nitrosourea alkylating agent, based on the hypothesis that chemotherapy-induced release of tumor antigens can enhance the efficacy of immunotherapy. The study included patients with metastatic melanoma with and without brain metastasis. With a median follow-up of 40 months, the 20 patients with brain metastases had 2- and 3-year brain PFS rates of 35% and 25%, respectively. The median OS and 3-year survival rates for patients with MBM were 12.7 months and 27.8%, respectively. These findings provided evidence for the first time that long-term survival rates and ORRs can also be attainable in a good percentage of patients with MBM.[56] Based on the promising data from NIBIT-M1, the NIBIT-M2 trial was initiated to further explore the role of ipilimumab in MBM. NIBIT-M2 followed a similar design to NIBIT-M1, but added a third arm that received ipilimumab in combination with the anti–programmed death 1 (anti–PD-1) monoclonal antibody nivolumab (Opdivo, Bristol Myers Squibb). The combination of ipilimumab and nivolumab produced a statistically significant improvement in OS in patients with MBM when compared with the ipilimumab and fotemustine combination, with a median OS of 29.2 months and 8.2 months, respectively (P=.009).[57] Kluger and colleagues enrolled 23 patients with asymptomatic MBM not requiring corticosteroids and reported durable response and acceptable toxicity with pembrolizumab (Keytruda, Merck), another anti–PD-1 monoclonal antibody, in this patient population. The intracranial response rate was 22%, and 48% of patients remained alive at 24 months.[58]

The efficacy reported in single-agent immunotherapy studies for ipilimumab, nivolumab, and pembrolizumab, on one hand, and the benefit of ipilimumab combinations, on the other, led to other trials that investigated the efficacy of combination immunotherapy in MBM.[59-61] In fact, the most promising immunotherapy regimen for MBM to date is the combination of ipilimumab and nivolumab.

The CheckMate 204 trial by Tawbi and colleagues was an open-label phase 2 study that included 101 patients with untreated asymptomatic MBM (cohort A) and 18 patients with untreated symptomatic MBM (cohort B). Patients were given a combination of ipilimumab and nivolumab. Recently published results from the final 3-year follow-up showed investigator-assessed intracranial clinical benefit in 58 (57.4%) of 101 patients in cohort A and in 3 (16.7%) of 18 patients in cohort B. An investigator-assessed objective response was observed in 54 (53.5%) patients in cohort A and 3 (16.7%) patients in cohort B. The 36-month intracranial PFS rate was 54.1% and 18.9% for cohorts A and B, respectively, and the 36-month OS rate was 71.9% and 36.6%, respectively. The most common treatment-related adverse events were increased alanine aminotransferase and aspartate aminotransferase. No grade 3 adverse events were observed in more than 1 patient each in cohort B and no grade 4 adverse events occurred. The durable 3-year intracranial response, PFS, and OS for asymptomatic MBM patients further supported the first-line use of the ipilimumab and nivolumab combination. The median intracranial PFS and OS for the symptomatic MBM cohort, however, suggest limited activity in MBM patients who have neurologic symptoms and/or require corticosteroids, and support the need for alternative regimens for these patients.[60-62]

The Australian ABC trial, an open-label phase 2 trial, enrolled 3 cohorts of patients with MBM. Patients with asymptomatic MBM who did not receive prior local brain therapy were randomly assigned to either cohort A, in which they received both nivolumab and ipilimumab followed by nivolumab, or cohort B, in which they received nivolumab. Patients who had brain metastases that failed local therapy, neurologic symptoms, and/or leptomeningeal disease were included in the nonrandomized cohort C and received nivolumab. The 5-year intracranial PFS rate was 46% for the combination group compared with only 15% and 6% for cohorts B and C, respectively. The study design allowed treatment with prior targeted therapy, and patients who were naive to BRAF and MEK inhibitors had a better response rate.[59]

Combination Immunotherapy and Targeted Therapy

Combination therapy is usually the favored approach to drug-resistant malignancies. As such, combining checkpoint inhibitors with BRAF inhibitors aimed at improving the antitumor response merits evaluation.[63] Oncogenic BRAF can induce an immune inhibitory phenotype that promotes the escape of melanoma cells from the immune system. For example, the *BRAF* V600 mutation promotes the production of immuno-inhibitory factors such as interleukin 6 (IL-6), IL-10, and vascular

endothelial growth factor; decreases the expression of major histocompatibility complex (MHC) class I molecules; and decreases the CD4/CD8 T-cell ratio and the number of natural killer cells.[63,64] BRAF inhibitors, on the other hand, can promote the expression of PD-1 in melanoma cells, and the addition of MEK inhibitors did not compromise T-lymphocyte recruitment.[63,64] Using SM1, a mouse model of *BRAF* V600–mutated melanoma, the addition of the MEK inhibitor trametinib enhanced the antitumor activity of immunotherapy when combined with the BRAF inhibitor dabrafenib, as evidenced by increased melanosomal antigens and MHC expression and global immune-related gene upregulation.[64] This in vitro data, combined with the aim of achieving a more rapid response with BRAF/MEK inhibitors and a more durable response with immunotherapy, led to trials that evaluated the combination of a BRAF/MEK inhibitor with immunotherapy in MBM.

Initial data showed hepatotoxicity from the combination of vemurafenib and ipilimumab. A phase 1 study by Ribas and colleagues evaluated the safety of this combination. Patients who had MBM that harbored a *BRAF* V600 mutation and who did not receive prior therapy with a BRAF/MEK inhibitor nor with anti–CTLA-4 monoclonal antibodies were eligible. The first cohort included 6 patients who received both medications at full dose: 1 month of vemurafenib at 960 mg orally twice daily, followed by 4 doses of ipilimumab at 3 mg/kg every 3 weeks and concurrent vemurafenib. The second cohort included 6 patients who were given a lower dose of vemurafenib (720 mg orally twice daily) followed by full-dose ipilimumab. Four patients from the first cohort had grade 3 elevations in aminotransferase levels at 2 to 5 weeks from the first ipilimumab dose, and 4 patients from the second cohort also developed grade 2 to 3 elevations within 3 weeks of the first ipilimumab dose. Following this reported hepatotoxicity, the study was closed to further accrual of patients.[65]

The first published phase 3 trial that evaluated the first-line combination of BRAF/MEK inhibitors and immune checkpoint inhibitors in metastatic *BRAF*-mutated melanoma was IMspire150. Patients with untreated or actively progressing brain metastases were excluded, and patients with previously treated brain metastases were included (n=13). Patients were randomly assigned to the vemurafenib/cobimetinib plus atezolizumab (Tecentriq, Genentech) group or the vemurafenib/cobimetinib plus placebo group. The atezolizumab group had a similar ORR compared with the placebo group (66.3% vs 65%, respectively). However, the atezolizumab group had a significant improvement in PFS compared with the placebo group (15.1 months vs 10.6 months, respectively). No data have been published regarding the intracranial response of the subgroup of patients who had brain metastases.[66]

A phase 2 trial called TRICOTEL is investigating the safety and efficacy of atezolizumab, cobimetinib, and vemurafenib in patients with *BRAF*-mutated melanoma and brain metastases (NCT03625141). The study includes 2 cohorts: cohort 1 consists of patients who are *BRAF*–wild type and cohort 2 consists of patients who are *BRAF*-mutated. Both cohorts consist of patients with central nervous system lesions of at least 5 mm, and concomitant use of corticosteroids or anticonvulsants is allowed. Cohort 1 is receiving atezolizumab and cobimetinib, whereas cohort 2 is receiving atezolizumab and cobimetinib in addition to vemurafenib. The primary endpoint of the study is the ORR, and 80 patients have been recruited.[67,68] Following the primary analysis of the IMspire170 study, which showed no benefit for atezolizumab and cobimetinib compared with pembrolizumab in *BRAF*–wild type melanoma, cohort 1 was closed with 15 patients recruited at that time.[67,69] The IMspire170 study was an open-label phase 3 study that randomly assigned 446 patients to 1 of 2 groups: cobimetinib plus atezolizumab (n=222) or pembrolizumab alone (n=224).[69] Primary results from the TRICOTEL study were presented at the 2022 annual meeting of the American Society of Clinical Oncology (ASCO). Investigator-assessed intracranial outcomes for cohort 1 showed an ORR of 27% and a median PFS of 2.2 months. Cohort 2, which included 65 patients, had an ORR of 42% and a median intracranial PFS of 5.8 months. Interestingly, symptomatic patients from cohort 2 had a significant intracranial ORR of 58% as evaluated by the investigators. Of 11 patients receiving corticosteroids, 6 patients discontinued or tapered this treatment during cycle 1. This study supports the triplet combination of atezolizumab, cobimetinib, and vemurafenib for patients with *BRAF*-mutated MBM as a possible standard-of-care option. Because this recommendation is based on a single arm of a study with a relatively modest number of patients in the face of ongoing trials of other options, however, it remains premature. Of particular interest are the intracranial results for symptomatic patients, who represent an area of unmet need, and the possibility of reducing corticosteroid use with cobimetinib and vemurafenib, thus increasing the benefit from the subsequent addition of atezolizumab.[70,71] Ongoing trials are also studying the combination of targeted therapy and immunotherapy. The TRIDeNT trial, for example, is studying the combination of nivolumab, dabrafenib, and trametinib in 26 patients with *BRAF*-mutated metastatic melanoma, including those with MBM.[72]

In line with combination therapy options, a meta-analysis of randomized phase 2 and 3 trials by Ferrucci and colleagues evaluated triplet combinations of immunotherapy and targeted therapy for *BRAF*-mutated

metastatic melanoma. The authors presented their results at the 2022 annual meeting of ASCO, with data from 3 independent trials included. There was a significant 23% decrease in the risk of progression and a 21% decrease in the risk of death, yet there was no difference in the ORR observed between the arms. In addition, there was an increase in the frequency of grade 3 or higher adverse events, with more events occurring with triplet therapy as compared with targeted therapy alone. This meta-analysis further emphasized that there remains a need for biomarker-driven studies that can identify the patient population who can benefit the most from triplet therapy.[73]

On the other hand, the phase 3 DREAMseq trial compared the efficacy and toxicity of the sequence of nivolumab/ipilimumab followed by dabrafenib/trametinib with the converse sequence in treatment-naive *BRAF*-mutated metastatic melanoma. According to results presented at the 2022 annual meeting of ASCO, the 3-year OS was superior in the treatment sequence beginning with immunotherapy vs the arm starting with dabrafenib/trametinib, at 66.2% vs 42.8%, respectively. The median PFS for the arm beginning with immunotherapy was not reached, whereas that of the latter arm was 12.7 months. It is worth noting that patients with brain metastases consisted of 62% and 58% of each arm, respectively, and that crossover was frequently not feasible, in many cases owing to ineligibility caused by progression of central nervous system metastases. In fact, the presence of brain metastases—which respond markedly to immunotherapy—may be largely responsible for the observed difference between the 2 arms, with the greater benefit seen in patients who received immunotherapy first.[74]

Stereotactic Radiosurgery With Targeted Therapy/Immunotherapy

Combining the ablative pro-apoptotic effect of SRS with the immunomodulatory effect of immunotherapy may lead to improved local control in MBM. Several retrospective studies and data from a few prospective studies have explored the efficacy of this combination and showed excellent intracranial response rates.[2] A study by Knisely and colleagues prospectively collected data from 77 patients with MBM who received ipilimumab with SRS. The addition of ipilimumab to SRS was associated with an improved median OS from 4.9 months to 21.3 months.[74]

Data also have shown improved brain tumor local control and OS with the use of SRS and BRAF/MEK inhibitors, therefore suggesting the possibility of increased intracranial delivery of these drugs owing to SRS. An analysis by Ahmed and colleagues of 96 patients with MBM who received SRS within 3 months of systemic therapy—namely anti–PD-1 agents, anti–CTLA-4 agents, and BRAF/MEK inhibitors—showed a significantly improved OS when compared with conventional chemotherapy.[75] Attention should be paid, however, to the risk for radiation necrosis with concurrent use of BRAF/MEK inhibitors and SRS. Although a scarcity of data exists regarding the timing of withholding BRAF/MEK inhibitors and SRS, oncologists generally withhold therapy for 3 to 5 days around the time of SRS treatment.[75,76]

Interestingly, radiation-induced apoptosis of tumor cells is associated with an antitumor immune response that can result in regression of tumors distant from those that received radiation therapy, which is referred to as the abscopal effect. The abscopal effect has been reported in several studies of the combination of anti–CTLA-4 inhibitors and radiation therapy.[77] The optimal sequence of systemic therapy and SRS still needs to be further investigated by prospective studies.[2,78]

Conclusions

In conclusion, as the incidence of metastatic melanoma continues to rise, identifying the optimal therapeutic options for MBM becomes increasingly important. Brain metastases are associated with significant disease-related morbidity and mortality. Management of this devastating disease has been revolutionized during the past decade, particularly with the advent of targeted therapy and immunotherapy, along with improved local therapeutic options such as SRS. It is important to emphasize the role of patient-centered individualized care when managing those with MBM. This can be implemented through a multidisciplinary approach that involves the medical oncologist, radiation oncologist, neurosurgeon, and neuroradiologist.[2]

Surgery should be considered for patients with symptomatic and large MBM, whereas SRS is considered for patients with 1 to 4 brain lesions. SRS can be used as an alternative to surgery for lesions that are no larger than 3 cm in diameter and deep, and therefore not amenable to surgery. In patients with MBM who have symptoms caused by a pressure effect exerted by large brain metastases, upfront surgical resection followed by SRS to the surgical bed is warranted.[2,13,14,27] Combination immunotherapy has led to durable intracranial response, PFS, and OS for patients with asymptomatic MBM.

The impressive intracranial activity of targeted therapy and immunotherapy in patients with MBM warrants consideration for upfront systemic therapy. Although the optimal sequence of therapeutic modalities remains an area of active investigation, these data strongly suggest that treatment decisions should be made in a multidisciplinary

setting, and that the decision of which modality to deploy first should be personalized to the patient's presentation, extent of disease, and prior therapies in order to optimize clinical outcome.

Novel combinations of treatments are being explored. Although we are still awaiting results from ongoing trials, the data available to date have shown that patients with MBM can have a response and OS that are similar to those with no brain metastases. Investigators and pharmaceutical companies should be encouraged to include patients with MBM in all phases of clinical research, from phase 1 to phase 3 trials, in order to accelerate drug development for this population, which is in dire need of improved therapies.

Disclosures

Dr Kreidieh has no conflicts of interest to disclose. Dr Tawbi has received grants or research support from Bristol Myers Squibb, Novartis, Merck, Genentech, GlaxoSmithKline, EMD Serono, Eisai, Dragonfly Therapeutics, and RAPT Therapeutics, and has served as a paid consultant to Bristol Myers Squibb, Genentech, Novartis, Merck, Boxer Capital, Karyopharm, Iovance, Eisai, Jazz Pharmaceuticals, and Medicenna.

References

1. Melanoma of the skin: at a glance. Cancer Statistics Center, American Cancer Society. https://cancerstatisticscenter.cancer.org/#!/cancer-site/Melanoma%20of%20the%20skin. Accessed Feb 9, 2022.
2. Rishi A, Yu HM. Current treatment of melanoma brain metastasis. *Curr Treat Options Oncol*. 2020;21(6):45.
3. Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. *Cancer*. 2011;117(8):1687-1696.
4. Tawbi HA, Boutros C, Kok D, Robert C, McArthur G. New era in the management of melanoma brain metastases. *Am Soc Clin Oncol Educ Book*. 2018;38:741-750.
5. Sampson JH, Carter JH Jr, Friedman AH, Seigler HF. Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. *J Neurosurg*. 1998;88(1):11-20.
6. Sloot S, Chen YA, Zhao X, et al. Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. *Cancer*. 2018;124(2):297-305.
7. Frinton E, Tong D, Tan J, et al. Metastatic melanoma: prognostic factors and survival in patients with brain metastases. *J Neurooncol*. 2017;135(3):507-512.
8. Carapella CM, Gorgoglione N, Oppido PA. The role of surgical resection in patients with brain metastases. *Curr Opin Oncol*. 2018;30(6):390-395.
9. Fischer GM, Jalali A, Kircher DA, et al. Molecular profiling reveals unique immune and metabolic features of melanoma brain metastases. *Cancer Discov*. 2019;9(5):628-645.
10. Fife KM, Colman MH, Stevens GN, et al. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol*. 2004;22(7):1293-1300.
11. Wasif N, Bagaria SP, Ray P, Morton DL. Does metastasectomy improve survival in patients with stage IV melanoma? A cancer registry analysis of outcomes. *J Surg Oncol*. 2011;104(2):111-115.
12. 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. *Oncologist*. 2019;24(5):671-679.
13. Gazzeri R, Nalavenkata S, Teo C. Minimally invasive key-hole approach for the surgical treatment of single and multiple brain metastases. *Clin Neurol Neurosurg*. 2014;123:117-126.
14. Hatiboglu MA, Wildrick DM, Sawaya R. The role of surgical resection in patients with brain metastases. *Ecancermedicalscience*. 2013;7:308.
15. Gupta S, Dawood H, Giantini Larsen A, et al. Surgical and peri-operative considerations for brain metastases [published online May 5, 2021]. *Front Oncol*. doi:10.3389/fonc.2021.662943.
16. Ene CI, Ferguson SD. Surgical management of brain metastasis: challenges and nuances. *Front Oncol*. 2022;12:847110-847110.
17. Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014.
18. Morris SL, Low SH, A'Hern RP, et al. A prognostic index that predicts outcome following palliative whole brain radiotherapy for patients with metastatic malignant melanoma. *Br J Cancer*. 2004;91(5):829-833.
19. de la Fuente M, Beal K, Carvajal R, Kaley TJ. Whole-brain radiotherapy in patients with brain metastases from melanoma. *CNS Oncol*. 2014;3(6):401-406.
20. Trifiletti DM, Larner JM, Sheehan JP. When should patients with brain metastases receive whole brain irradiation? *J Radiosurg SBRT*. 2016;4(1):1-3.
21. Brown PD, Pugh S, Laack NN, et al; Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol*. 2013;15(10):1429-1437.
22. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol*. 2014;32(34):3810-3816.
23. Gondi V, Hermann BP, Mehta MP, Tomé WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. *Int J Radiat Oncol Biol Phys*. 2012;83(4):e487-e493.
24. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. *Nat Med*. 2002;8(9):955-962.
25. Doss LL, Memula N. The radioresponsiveness of melanoma. *Int J Radiat Oncol Biol Phys*. 1982;8(7):1131-1134.
26. Susko MS, Garcia MA, Ma L, et al. Stereotactic radiosurgery to more than 10 brain metastases: evidence to support the role of radiosurgery for ideal hippocampal sparing in the treatment of multiple brain metastases. *World Neurosurg*. 2020;135:e174-e180.
27. Yamamoto M, Kawabe T, Sato Y, et al. Stereotactic radiosurgery for patients with multiple brain metastases: a case-matched study comparing treatment results for patients with 2-9 versus 10 or more tumors. *J Neurosurg*. 2014;121(suppl):16-25.
28. Rava P, Leonard K, Sioshansi S, et al. Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery. *J Neurosurg*. 2013;119(2):457-462.
29. Ewend MG, Morris DE, Carey LA, Ladha AM, Brem S. Guidelines for the initial management of metastatic brain tumors: role of surgery, radiosurgery, and radiation therapy. *J Natl Compr Canc Netw*. 2008;6(5):505-513.
30. Liew DN, Kano H, Kondziolka D, et al. Outcome predictors of gamma knife surgery for melanoma brain metastases. Clinical article. *J Neurosurg*. 2011;114(3):769-779.
31. Muacevic A, Wowra B, Siefert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the brain: a randomized controlled multicentre phase III trial. *J Neurooncol*. 2008;87(3):299-307.
32. Rades D, Bohlen G, Pluemer A, et al. Stereotactic radiosurgery alone versus resection plus whole-brain radiotherapy for 1 or 2 brain metastases in recursive partitioning analysis class 1 and 2 patients. *Cancer*. 2007;109(12):2515-2521.
33. Sneed PK, Suh JH, Goetsch SJ, et al. A multi-institutional review of radiosurgery alone vs. radiosurgery with whole brain radiotherapy as the initial management of brain metastases. *Int J Radiat Oncol Biol Phys*. 2002;53(3):519-526.
34. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol*. 2011;29(2):134-141.
35. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009;10(11):1037-1044.
36. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316(4):401-409.

37. Becco P, Gallo S, Poletto S, et al. Melanoma brain metastases in the era of target therapies: an overview. *Cancers (Basel)*. 2020;12(6):1640.
38. 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.
39. 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.
40. 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.
41. Harding JJ, Catalanotti F, Munhoz RR, et al. A retrospective evaluation of vemurafenib as treatment for BRAF-mutant melanoma brain metastases. *Oncologist*. 2015;20(7):789-797.
42. Gorka E, Fabó D, Gézsi A, Czirbesz K, Fedorcsák I, Liszkay G. Dabrafenib therapy in 30 patients with melanoma metastatic to the brain: a single-centre controlled retrospective study in Hungary. *Pathol Oncol Res*. 2018;24(2):401-406.
43. Dzienis MR, Atkinson VG. Response rate to vemurafenib in patients with B-RAF-positive melanoma brain metastases: a retrospective review. *Melanoma Res*. 2014;24(4):349-353.
44. Gibney GT, Gauthier G, Ayas C, et al. Treatment patterns and outcomes in BRAF V600E-mutant melanoma patients with brain metastases receiving vemurafenib in the real-world setting. *Cancer Med*. 2015;4(8):1205-1213.
45. Martin-Algarra S, Hinshelwood R, Mesnage S, et al. Effectiveness of dabrafenib in the treatment of patients with BRAF V600-mutated metastatic melanoma in a named patient program. *Melanoma Res*. 2019;29(5):527-532.
46. Geukes Foppen MH, Boogerd W, Blank CU, van Thienen JV, Haanen JB, Brandsma D. Clinical and radiological response of BRAF inhibition and MEK inhibition in patients with brain metastases from BRAF-mutated melanoma. *Melanoma Res*. 2018;28(2):126-133.
47. Drago JZ, Lawrence D, Livingstone E, et al. Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study. *Melanoma Res*. 2019;29(1):65-69.
48. Holbrook K, Lutzky J, Davies MA, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. *Cancer*. 2020;126(3):523-530.
49. Seghers AC, Wilgenhof S, Lebbé C, Neyns B. Successful rechallenge in two patients with BRAF-V600-mutant melanoma who experienced previous progression during treatment with a selective BRAF inhibitor. *Melanoma Res*. 2012;22(6):466-472.
50. Viñal D, Martinez D, Espinosa E. Efficacy of rechallenge with BRAF inhibition therapy in patients with advanced BRAFV600 mutant melanoma. *Clin Transl Oncol*. 2019;21(8):1061-1066.
51. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF-directed treatment in metastatic melanoma: a multi-institutional retrospective study. *Eur J Cancer*. 2018;91:116-124.
52. Cagney DN, Alexander BM, Hodi FS, Buchbinder EI, Ott PA, Aizer AA. Rapid progression of intracranial melanoma metastases controlled with combined BRAF/MEK inhibition after discontinuation of therapy: a clinical challenge. *J Neurooncol*. 2016;129(3):389-393.
53. Hodi FS, Oble DA, Drappatz J, et al. CTLA-4 blockade with ipilimumab induces significant clinical benefit in a female with melanoma metastases to the CNS. *Nat Clin Pract Oncol*. 2008;5(9):557-561.
54. Schartz NE, Farges C, Madelaine I, et al. Complete regression of a previously untreated melanoma brain metastasis with ipilimumab. *Melanoma Res*. 2010;20(3):247-250.
55. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012;13(5):459-465.
56. Di Giacomo AM, Ascierto PA, Queirolo P, et al. Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian Network for Tumor Biotherapy (NIBIT)-M1 phase II study. *Ann Oncol*. 2015;26(4):798-803.
57. Di Giacomo AM, Sileni VC, Del Vecchio M, et al. Efficacy of ipilimumab plus nivolumab or ipilimumab plus fotemustine vs fotemustine in patients with melanoma metastatic to the brain: primary analysis of the phase III NIBIT-M2 trial [ESMO abstract 1081MO]. *Ann Oncol*. 2020;31(4)(suppl).
58. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol*. 2019;37(1):52-60.
59. Long GV, Atkinson V, Lo S, et al. Five-year OS from the anti-PD1 brain collaboration (ABC Study): randomized phase 2 study of nivolumab (nivo) or nivo+ ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets) [ASCO abstract 9508]. *J Clin Oncol*. 2021;39(15)(suppl).
60. 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.
61. Tawbi HA, Forsyth PA, Hodi FS, et al. Safety and efficacy of the combination of nivolumab plus ipilimumab in patients with melanoma and asymptomatic or symptomatic brain metastases (CheckMate 204). *Neuro Oncol*. 2021;23(11):1961-1973.
62. Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2021;22(12):1692-1704.
63. Mandalà M, De Logu F, Merelli B, Nassini R, Massi D. Immunomodulating property of MAPK inhibitors: from translational knowledge to clinical implementation. *Lab Invest*. 2017;97(2):166-175.
64. Hu-Lieskovan S, Mok S, Homet Moreno B, et al. Improved antitumor activity of immunotherapy with BRAF and MEK inhibitors in BRAF(V600E) melanoma. *Sci Transl Med*. 2015;7(279):279ra41.
65. Ribas A, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med*. 2013;368(14):1365-1366.
66. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced $BRAF^{V600}$ mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395(10240):1835-1844.
67. Queirolo P, de la Cruz Merino L, Abajo Guijarro A, et al. A phase II study evaluating atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with BRAF-mutant melanoma and central nervous system (CNS) metastases (mets) [ASCO abstract TPS10081]. *J Clin Oncol*. 2020;38(15)(suppl).
68. ClinicalTrials.gov. 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. https://www.clinicaltrials.gov/ct2/show/NCT03625141. Identifier: NCT03625141. Accessed February 5, 2022.
69. Gogas H, Dréno B, Larkin J, et al. Cobimetinib plus atezolizumab in $BRAF^{V600}$ wild-type melanoma: primary results from the randomized phase III IMspire170 study. *Ann Oncol*. 2021;32(3):384-394.
70. Dummer R, Queirolo P, Abjajo Guijarro AM, et al. Atezolizumab (A), cobimetinib (C), and vemurafenib (V) in patients (pts) with BRAF V600 mutation–positive melanoma with central nervous system (CNS) metastases (mets): primary results from phase 2 Tricotel study [ASCO abstract 9515]. *J Clin Oncol*. 2022;40(16)(suppl).
71. Dummer R, Queirolo P, Abajo Guijarro AM, 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*. 2022;23(9):1145-1155.
72. Tawbi H. The standard of care for brain metastases in melanoma. *Clin Adv Hematol Oncol*. 2020;18(1):28-31.
73. Ferrucci PF, Gaeta A, Cocorocchio E, et al. Meta-analysis of randomized phase II-III trials evaluating triplet combinations of immunotherapy and targeted therapy for BRAF V600-mutant unresectable or metastatic melanoma [ASCO abstract 9541]. *J Clin Oncol*. 2022;40(16)(suppl).
74. Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): a phase III trial—ECOG-ACRIN EA6134 [ASCO abstract 356154]. *J Clin Oncol*. 2021;39(36)(suppl).
75. Ahmed KA, Abuodeh YA, Echevarria MI, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy. *Ann Oncol*. 2016;27(12):2288-2294.
76. Acharya S, Mahmood M, Mullen D, et al. Distant intracranial failure in melanoma brain metastases treated with stereotactic radiosurgery in the era of immunotherapy and targeted agents. *Adv Radiat Oncol*. 2017;2(4):572-580.
77. Liu Y, Dong Y, Kong L, Shi F, Zhu H, Yu J. Abscopal effect of radiotherapy combined with immune checkpoint inhibitors. *J Hematol Oncol*. 2018;11(1):104.
78. Kroeze SG, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. *Cancer Treat Rev*. 2017;53:25-37.