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Skin Cancer (T Ito, Section Editor)

Current Treatment of Melanoma Brain Metastasis

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Opinion statement

With greater understanding of underlying biology and development of effective BRAF-targeted therapy and immunotherapy, along with remarkable advances in local treatment such as stereotactic radiosurgery, melanoma brain metastasis (MBM) is witnessing continually improving outcome, with 1-year overall survival rate approaching 85%. Given disease complexity and myriad treatment options, all patients with MBM should ideally be evaluated in a multidisciplinary setting to allow an individualized treatment approach based on prognostic groups, molecular classification, number and size of brain metastasis, and performance status. With improving outcome, pendulum has now swayed to focus more on effective treatment modalities with minimal neurological toxicity while maintaining quality of life. Surgery is usually considered in symptomatic and large MBMs, while stereotactic radiosurgery considered in 1–4 lesions, and now also being explored for up to 15 brain metastases for improved local control. The role of whole brain radiotherapy is diminishing given its neurocognitive toxicities and is reserved for patients with diffuse brain involvement. Cytotoxic chemotherapy has largely been ineffective without evidence for survival benefit. Immune checkpoint inhibitors have become the cornerstone of management for melanoma brain metastasis with durable intracranial tumor control and excellent toxicity profile. For patients with asymptomatic MBMs, ipilimumab and nivolumab have shown intracranial response near 60% and provides comparable clinical benefit in MBMs as for extracranial metastases. For patients with driver BRAF mutation, BRAFi-/MEKi-targeted agents are proven to be effective in MBM with high rate intracranial responses (44–59%). However, the durability of intracranial responses induced by BRAFi/MEKi seems to be shorter than that of extracranial disease. Emerging data support novel combination of systemic therapy and stereotactic radiosurgery, which appears to be safe and effective; however, potential benefits and risks should be evaluated prospectively. Promising ongoing trials will further expand therapeutic evidence in MBM, and patients should be encouraged to participate in clinical trials.

Introduction

Malignant melanoma is an aggressive skin malignancy with estimated age-standardized incidence rates of 3 per 100,000, which is rising worldwide [1, 2]. Melanoma exhibits profound brain-specific tropism and is the third most common origin of brain metastases after lung and breast cancers. It is estimated that up to 60% of all patients with metastatic melanoma will develop brain metastasis during the course of their disease, including 25% with solitary brain metastasis, which may contribute significantly to disease-related morbidity and mortality [3, 4]. Historically, patients with melanoma brain metastasis (MBM) had a uniformly dismal prognosis with a median survival of less than 3–6 months [4]. However, development of novel systemic therapies, such as BRAF-targeted therapy and immunotherapy, and advancement in local therapy, such as stereotactic radiosurgery (SRS) and surgical techniques, have all collectively improved the outcome with MBM to a median survival of 1–2 years [5, 6]. Herein, we discuss the understanding and current management of MBM.

Biology and risk factors

Brain metastasis is an intricate, multistep process, originating and escaping from primary cancer that extravasate through the basement membrane into systemic circulation, survive in circulation, adhere to local brain vasculature, invade blood–brain barrier, extravasate through microenvironment, and thrive by angiogenesis to establish into a brain metastasis [7]. Various receptor and protein molecules are overexpressed in melanoma cells that can lead to high brain tropism and are strongly implicative in MBM formation; these include chemokine receptor type 4 (CCR4), tetraspanins, integrins, melanotransferrin, and S100A4 protein [8, 9]. Protein kinase B (AKT)/phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) are the two parallel pathways that regulate cell survival and proliferation, and are strongly implicated in MBM as well [10]. Activation of the PI3K/AKT pathways is also known to mediate both de novo and acquired resistance to BRAF and MEK inhibitors [11].

Various studies identified risk factors for the development of brain metastasis, which include male sex; age>60 years; melanomas arising on mucosal surfaces or the skin of the trunk, head, neck, or scalp; deeply invasive or ulcerated primary lesions; acral, lentiginous, or nodular histology; involvement of >3 regional nodes at diagnosis or relapse; and visceral metastasis [12–14]. Molecular markers associated with MBM development include BRAF and NRAS mutation, expression of CCR4 on melanoma cells, and activation of the PI3K/AKT pathway [8, 15].

Predictors of survival in melanoma brain metastasis

To cluster patients with brain metastasis into similar prognostic groups, Gaspar et al. [16] published a seminal report and introduced Radiation Therapy Oncology Group's (RTOG) recursive partitioning analysis (RPA) using pooled data of 1200 patients from three consecutive RTOG brain metastasis randomized trials. Based on three factors (Karnofsky Performance Score (KPS), status of extracranial disease, and patient age), patients were divided into 3 prognostic groups. The best survival (median, 7.1 months) was observed in class 1 patients

<65 years of age with a KPS≥70 and a controlled primary tumor with the brain as the only site of metastases. The worst survival (median, 2.3 months) was seen in class 3 patients with a KPS<70. All other patients (class 2) had relatively minor differences in observed survival, with a median of 4.2 months.

One limitation of RTOG RPA model is that it is not disease specific, although this was validated in various diagnoses including melanoma patients which had median survivals of 151, 71, and 21 days for RPA classes 1, 2, and 3, respectively (p<0.001) [17]. Other limitations of RPA include omitting the number of brain metastases and estimating systemic disease control which was fraught with inconsistency due to variation in type and timing of imaging tests. Sperduto et al. [18] introduced graded prognostic assessment (GPA) using 4 factors—age, KPS, extracranial metastases (none and present), and number of metastases (1, 2–3, >3)—to more accurately determine the prognosis of patients with brain metastases. GPA was subsequently refined to diagnosis-specific GPA (DS-GPA); for melanoma, prognostic factors were KPS and number of brain metastases, with a low KPS and >3 brain metastases associated with poor outcome (median survival of 3.4 months) and a higher KPS with 1–3 metastases associated with better prognosis (median survival of 13.2 months) [19].

Recently, Sperduto et al. updated the DS-GPA specific for MBMs by including molecular markers (Melanoma-molGPA) in a larger and current cohort (n=823) diagnosed from 2006 to 2015. Melanoma-molGPA scores of 4.0 and 0.0 were associated with the best and worst prognoses, like DS-GPA indices. There were 5 significant prognostic factors for survival (age, KPS, extracranial metastases, number of brain metastases, and BRAF status), whereas only KPS and number of brain metastases were included in the original Melanoma-GPA. Using Melanoma-molGPA, median survival times for patients for scores 0–1, 1.5–2, 2.5–3, and 3.5–4 were 4.9, 8.3, 15.8, and 34.1 months, respectively [20••]. The development of such prognostic tools has facilitated clinical decision-making by helping physicians differentiate patients based on expected survival and also useful for stratification of clinical trials.

Approach to management

Management of melanoma brain metastasis involves multimodality approach and increasing personalized treatment planning, with the integration of systemic therapy combined with traditionally local therapy such as SRS and/or surgery. CNS is previously considered a sanctuary site that rendered systemic therapy ineffective due to poor BBB penetration. However, recent data have shown improved intracranial response with newer classes of systemic therapies such as BRAF/MAP kinase inhibitors (BRAFi/MEKi) and immunotherapy (anti-programmed cell death protein 1 or anti-PD1, anti-cytotoxic T lymphocyte–associated protein 4 or anti-CTLA-4). The choice of local therapy (surgery, SRS) depends on patient performance, location, size, metastasis-induced neurological symptoms, and number of brain metastasis. The advantages of surgery include rapid relief of pressure effect on surrounding normal brain structures and evacuation of intra- or peri-tumoral hemorrhage, as well as procurement of tissue for diagnosis and molecular studies to select appropriate systemic therapy. It is a frequent practice in patients with multiple MBM to combine surgery

for larger and symptomatic lesion(s), and SRS for the remainder lesions. Following resection, post-operative radiotherapy to resection cavity is recommended to improve local control by eliminating micrometastasis or residual metastasis. In the next sections, we describe each treatment modality and recent evidence that led to its present-day use.

Surgery

Surgical resection is a therapeutic option if metastasis is solitary or limited in number or symptomatic due to mass effect on the surrounding brain, and above all if located in a surgically accessible region [21]. Moreover, surgery can provide a tissue diagnosis to identify new genetic drivers to potentially guide appropriate systemic therapy, given a growing evidence that MBMs possess unique molecular characteristics compared with primary disease or metastases at other sites [22•]. Surgical resection of brain metastasis has been shown to improve overall survival in various studies [23, 24]. In a population study with >4200 patients, metastasectomy improved median (12 vs. 5 months) and 5-year overall survival (16% vs. 7%, $p<0.001$). Although the role of surgical resection is well established for solitary brain metastasis, in multiple brain metastases, the pendulum sways away from surgery towards radiotherapy as mainstay local treatment or used in combination with surgery. The number of lesions that can be safely removed depends primarily on safety and clinical justification. The selective patient population who underwent metastasectomy of multiple MBMs may have survival benefit, although there is insufficient prospective data to support this approach [23–25]. Generally, for patients with up to 3–4 brain metastases in accessible locations, good performance status (KPS>70), and controlled systemic disease, surgical resection may be a viable option [25, 26]. Depending on extent of excision and size and number of metastases, post-operative radiation therapy to resection cavity or whole brain radiation therapy is always recommended [27, 28].

Whole brain radiotherapy

Radiation therapy was traditionally delivered as whole brain radiotherapy (WBRT), especially for multiple MBMs. The rationale of WBRT is that it comprehensively treats both macroscopic and microscopic metastases in the brain. Nevertheless, prognosis is dismal, with the median overall survival following WBRT approximately 2–5 months, and 1-year survival less than 10–12% [6, 17, 29]. WBRT for MBM has played a central role for decades until recent years when stereotactic radiosurgery (SRS) was introduced. The role of WBRT is shrinking mainly due to its detrimental effect on neurocognition and quality of life and lack of survival benefit. Nevertheless, it continues to play an important role for palliation in patients who have numerous symptomatic brain metastases, extensive metastasis not amendable for radiosurgery, and symptomatic leptomeningeal carcinomatosis, and for those whose performance status is poor [30]. The most common used WBRT fractionation regimen is 30 Gy in 10 fractions or 20 Gy in 5 fractions delivered daily to the whole brain. Various interventions have been attempted to mitigate the WBRT-induced neurocognitive decline. The concomitant use of memantine hydrochloride, a non-competitive N-methyl-d-aspartate (NMDA)

receptor antagonist, has shown to be neuroprotective by binding to and inhibiting ion channels of NMDA receptors located in cortical and hippocampal neurons, thus preserving cognitive functions [31]. This was further investigated in a large (*n*=508) placebo-controlled trial (RTOG 0614) demonstrating that patients who received memantine during and following WBRT had lesser neurocognitive failure (53.8% vs. 64.9%) and reduced rate of decline in memory, executive function, and processing speed as compared with those who did not receive memantine [31]. Preclinical studies have demonstrated that modest doses of radiation can cause a significant decline in neurogenesis in the hippocampus in sub-granular zone which is associated with the suppression of new memory formation and impaired recall [32]. Studies have shown a dose-response relationship between radiation dose received by the hippocampus and risk of postradiotherapy decline in recent memory [33]. This incited growing interest of hippocampal-avoidance WBRT in reducing neurocognitive decline [34]. RTOG 0933, a single-arm multi-institutional phase II study, showed hippocampal-avoidance WBRT is associated with a better preservation of memory and QOL as compared with historical series [35]. NRG CC001, a recently reported phase III trial of WBRT (30 Gy in 10 fractions) plus memantine with or without hippocampal avoidance, showed better preservation of neurocognitive function and patient-reported symptoms, with similar intracranial control and survival. Authors recommended hippocampal avoidance WBRT should be considered a standard of care for patients with good performance status who receive WBRT for BM with no metastases in the hippocampal region [36, 37•]. WBRT may not provide long-term intracranial control, as many patients live longer with immunotherapy and/or targeted therapy and develop recurrence, and therefore, continued surveillance is recommended.

Stereotactic radiosurgery

With technological advancement in precision radiation oncology and imaging modalities such as high-resolution MRI in the last 2–3 decades, it became feasible to treat metastatic lesion(s) with a large ablative radiation dose, aka SRS, effectively and safely while sparing surrounding normal brain tissues. Melanoma being a radioresistant cancer, ablative dose with SRS has a strong radiobiological rationale for improved cell killing, and clinical studies since the 1990s has shown SRS as a very effective local therapy for MBMs [38]. SRS is currently the standard local therapy over WBRT for ≤4 brain metastases, and ongoing prospective trials are evaluating the role of SRS for 5–15 brain metastases [30, 39, 40]. In selective patients with 1–4 metastases measuring less than 3–4 cm, SRS yields an excellent local control with response rates of as high as 90%, median survival of 5–11 months, and 1-year survival of 25% [41, 42]. Although no large randomized study comparing surgery versus SRS, there are a few small randomized studies and retrospective series which showed SRS to be equally efficacious as surgery [43, 44]. A phase III randomized study of 33 patients, which was stopped prematurely due to poor accrual, compared Gamma Knife SRS alone versus surgery plus

WBRT in patients with a single, ≤3-cm brain metastasis and showed similar local tumor control [43]. Generally, SRS can be used as an alternative to surgery in patients with lesion size(s) of <3 cm each, deep tumor locations, minimal pressure symptoms or midline shift, or hydrocephalus, and in those who are unable to undergo surgery [41]. While existing evidence for the use of SRS for ≤4 brain metastases is sufficient, there are growing interest and studies for ≥10 lesions, including an ongoing phase III trial evaluating SRS for 5–15 brain metastases versus hippocampal-avoidance WBRT [30, 39, 40]. While effective with excellent local control of MBM up to 85–95%, randomized trials did not demonstrate improved overall survival following SRS treatment [45, 46]. Although patients treated with SRS alone are more likely to develop distant intracranial relapse, randomized and retrospective data did not show survival benefit when adding WBRT to SRS treatment [45–47]. The landmark Alliance trial (NCT00377156) randomized 213 patients to SRS alone vs. SRS + WBRT, which showed lesser cognitive deterioration (63.5% vs 28%) and better quality of life favoring SRS alone. Although the time to intracranial failure was significantly shorter for SRS as compared with SRS + WBRT, there was no difference in overall survival (p=0.9) [48••]. Therefore, SRS alone with imaging surveillance without WBRT has become a standard therapy for limited number of brain metastases ≤3 cm.

For larger size lesion (>3 cm) or close to vital structures (brain stem, optic chiasm), single-fraction SRS are associated with a higher risk of radiation injury [49]. In such cases, fractionated (3–5 fractions) stereotactic radiotherapy (FSRT) has been used to exploit differential radiation repair capacity of tumor and normal tissues, thus permitting treatment with a higher effective total dose while minimizing toxicity. FSRT has shown good local control of >85% in published studies, and ongoing prospective trials such as a dose-escalation phase I study for large unresectable lesions (NCT02054689) are underway [50, 51]. However, patients with large brain metastases are usually symptomatic due to pressure effect and may require upfront surgical decompression. Surgical resection followed by adjuvant SRS to the surgical cavity is highly effective, with 1-year local control of 70–90% [52–54]. While surgical cavities of large metastases may involute to a size amenable to treatment with single-fraction SRS (NCCTG N107C/CEC·3 study only included <5 cm cavity) [54], FSRT is often considered in cases where the cavity remains large. A randomized trial (NCT04114981) comparing post-op SRS and FSRT is being planned by Alliance for Clinical Trials in Oncology [55] (Fig. 1).

Systemic therapy

The impermeability of the BBB confers limited responses of MBMs to chemotherapeutic agents, and therefore, in the past decades, local therapies (surgery, WBRT, SRS) were the pillars of MBM management. However, with a better understanding of melanoma molecular biology, discoveries of driver mutations, and advances in immunotherapies and targeted therapies, there are evolving clinical evidence demonstrating considerable intracranial activity with these agents. Since 2011, the US Food and Drug Administration (FDA) has approved indication for 7 new drugs as systemic therapy of metastatic

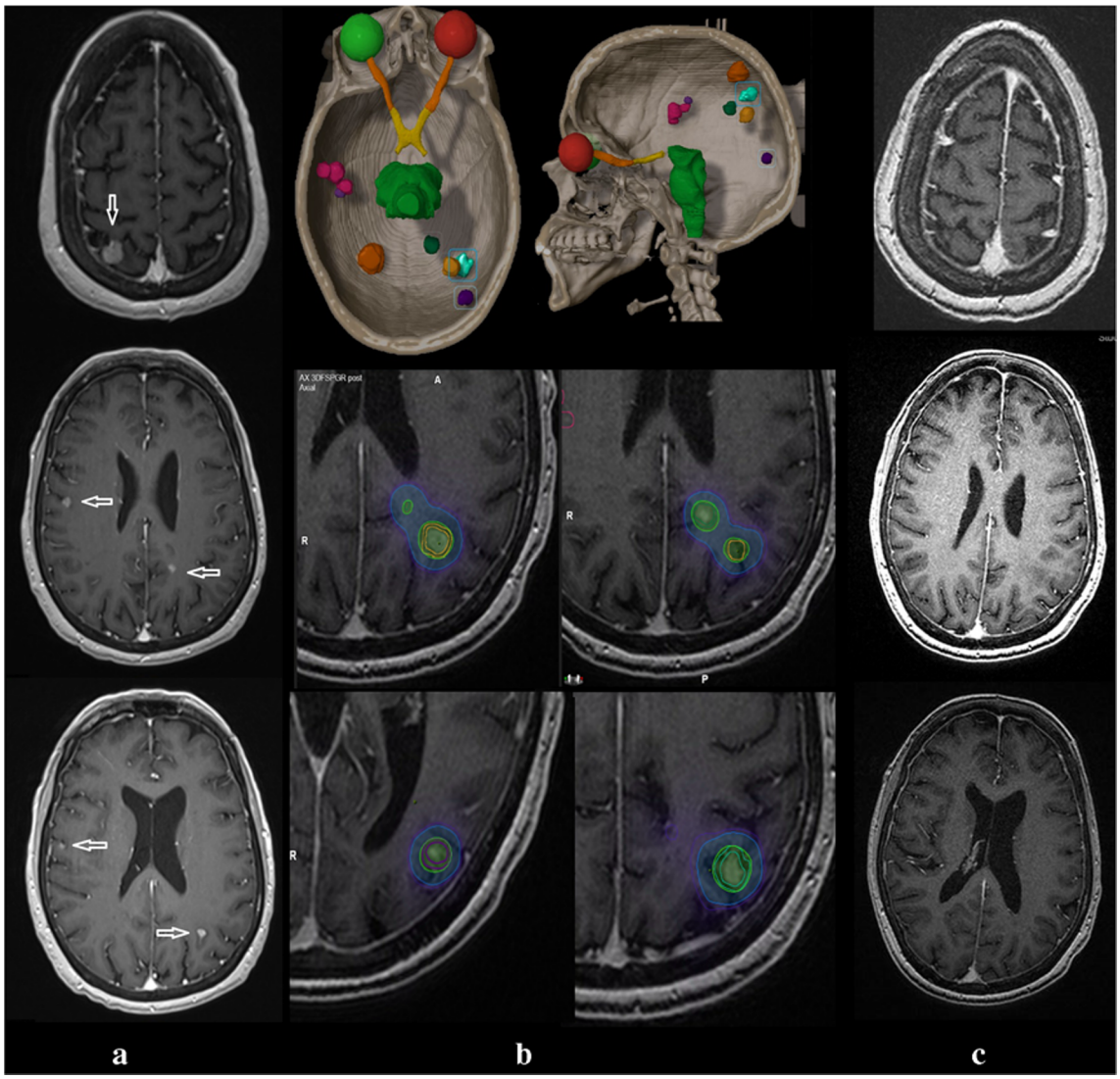

Fig. 1. Patient with 8 melanoma brain metastases was treated with stereotactic radiosurgery (SRS). **a** Baseline MRI showing metastatic lesions. **b** SRS planning with bird's-eye view and planning isodose lines. **c** Follow-up MRI after 5 months showing near complete resolution of all lesions. However, this patient developed new cerebellar lesion 8 months after initial SRS which was also treated with SRS

melanoma. For MBMs, these newer systemic therapies have been shown to have intracranial activities and in conjugation with local therapy may provide better intracranial control.

Cytotoxic chemotherapy

Larger chemotherapy molecules, including dacarbazine, a DNA-alkylating agent, which has long been historical standard cytotoxic chemotherapy for melanoma, are not able to cross the BBB to incite appropriate response for the management of MBMs. Not surprisingly, most studies exploring the role of

cytotoxic chemotherapy in MBMs, such as dacarbazine, temozolomide, paclitaxel, carboplatin, did not show survival advantage or intracranial response in metastatic melanoma [56–58]. Temozolomide, a derivative of dacarbazine which readily penetrates the blood–brain barrier to achieve cerebrospinal fluid concentration up to 30% of plasma, only demonstrated clinical responses in roughly 10% as a single agent or combined with WBRT or other agents [56].

Targeted therapy

Genetic mapping of melanoma identified approximately 50% of melanomas harboring the driver mutation in the serine-threonine protein kinase B-RAF (BRAF) gene resulting in uncontrolled activation of the MAPK pathway [59]. BRAF inhibition blocks the MAPK signaling pathway that normally promotes cell proliferation. In melanoma, over 90% BRAF mutations are at codon 600, and among them, >90% are BRAFV600E (substitution of glutamic acid for valine), followed by BRAFV600K (substituting lysine for valine), that represents 5–6% [60]. To date, three BRAF inhibitors—vemurafenib, dabrafenib, and encorafenib— (in combination with the MEK inhibitor binimetinib) have been FDA approved for metastatic melanoma. Mouse model showed lower CSF level of BRAF inhibitors which are substrates for the BBB drug efflux pumps leading to 2–3-fold lower concentration of targeted agent in CSF than plasma [61]. Vemurafenib has a much lower brain penetration than dabrafenib. However, BBB is frequently violated in MBM and intracranial response was observed in responding cancer [62].

The initial phase 1 and phase II studies established the safety profile of vemurafenib (PLX4032), the first potent BRAFV600 inhibitor, which showed overall response rate of 53% with median overall survival of 15.9 months [59, 63]. However, these early studies excluded patients with active brain metastases. Vemurafenib for brain metastasis has shown intracranial overall response rate of 18–50% in early studies [64, 65]. A phase I trial first established safety and efficacy of dabrafenib, another BRAFV600 inhibitor, for MBM in treatment-naive MBM demonstrating that nine of ten patients had reductions in size of brain lesions following dabrafenib, including four complete remissions [66]. This led to a larger open-label phase II BREAK-MB study evaluating efficacy of dabrafenib in 172 patients with BRAF mutated MBMs. Among BRAF V600E mutated patients, median survival of 33 weeks and overall intracranial response of 39.2% were noted in patients without prior local therapy; and median survival of 31.4 weeks and overall intracranial response of 30.8% were reported in patients with prior local treatment. Patients with a BRAF V600K mutation had substantially lower overall response rates; however, all patients had acceptable safety profile with dabrafinib [67]. Another study establishing efficacy of dabrafenib for intra- and extracranial metastasis showed high and statistically similar response rates for intracranial (78%) versus extracranial (90%) sites, with identical median site-specific progression-free survival [68].

The BRAF inhibitors show good single-agent activity with a promising initial response; however, resistance is almost a rule, secondary either to inadequate MAPK inhibition or reactivation of the MAPK pathway through preferential molecular mechanisms (MEK mutations, BRAF-splice mutants, NRAS-mutations, adaptive RTK signaling) [69, 70]. Therefore, it is the rationale for BRAF-MEK inhibitor combination therapy to target the PI3K-AKT pathway

concomitantly with MAPK inhibition. Combing BRAF/MEK inhibitors was supported by recent trials. A randomized trial of 423 untreated unresected stage IIIC and IV melanoma patients treated with dabrafenib and trametinib versus dabrafenib only showed median overall survival of 25.1 vs 18.7 months favoring dabrafenib and trametinib group (HR 0.71, p=0.01) and improved median progression-free survival (PFS) (11.0 months vs. 8.8 months (HR 0.67, p=0.0004)) [71]. For patients with MBM, results from COMBI-MB (NCT02039947) trial showed that dabrafenib–trametinib combination therapy had higher intracranial response (58%) than previously reported (39%, BREAK-MB study) single-agent BRAF therapy in patients with asymptomatic BRAF V600E-mutated MBM without prior local therapy [72••]. For symptomatic MBM patients vs. patients with prior local therapy, intracranial response rates were similar (59% vs. 56%). Encouragingly, response rate to BRAF-MEK inhibitor combination therapy in the brain was similar to that observed at extracranial sites and no additional brain-specific side effects were reported [72••]. Despite the promising results of these studies, the intracranial responses were relatively shorter than extracranial sites and the brain shown to be the major site of treatment failure [71]. This suggests a role for the brain microenvironment in therapeutic escape and BRAF-MEK inhibitor resistance. Various and emerging novel combination "parallel-pathway inhibition" treatment strategies are being explored to curb this resistance mechanism [73].

Immunotherapy

Melanoma is highly immunogenic cancer, with several reports of immune-mediated spontaneous regression [74]. High-dose interleukin-2 (IL-2) was the first immune therapy used in stage 4 melanoma patients. IL-2, a cytokine produced by activated T cells, causes proliferation of cytotoxic T cells, natural killer cells, and monocytes. High-dose IL-2 achieved overall response, including durable complete remission for a small percentage of metastatic melanoma patients (<10%) [75]. Unfortunately, IL-2 treatments were associated with severe toxicity and its efficacy against brain metastases was disappointing with 6% response rates in previously untreated MBMs [76]. The second immune drug approved by the FDA was interferon-α (IFN-α) and was associated with overall response rates of 22% and complete response <4%. However, responses of IFN- α were limited to patients with low-tumor burden and did not show efficacy against MBMs. The clinical benefit of IL-2 and INF-α has provided the "prototype concept" for further research to establish the role of immunotherapy in metastatic melanoma.

Adoptive cell therapy entails harvesting lymphocytes from the melanoma patients either from blood or tumor-infiltrating lymphocytes, followed by in vitro selection, expansion (with or without genetic manipulation) and their activation with subsequent re-infusion of these processed lymphocytes into patients after lymphodepletion to induce an immune antimelanoma responses. A study of 26 patients with treatment-naïve MBMs showed 7 patients (41%) achieved intracranial complete response following adoptive cell therapy with tumor-infiltrating lymphocytes [77]. The flipside of adoptive cell therapy is inhibitory cost, limited availability, and complexity involved in the development of these "custom-made therapy" with the duration of in vitro culture, skilled man-hours, and patient preparation for lymphodepletion with high-

dose chemotherapy and/or total body irradiation. Not surprisingly, despite these encouraging results, adoptive cell therapy has largely been replaced by newer class of immunotherapy such as checkpoint inhibitors in the treatment of metastatic melanoma.

In 1987, James P. Allison identified cytotoxic T lymphocyte antigen 4 (CTLA-4), a key negative regulator preventing T cells from attacking tumor cells, and in the 1990s, Okazaki et al. discovered a molecule on T cells called programmed death 1 (PD-1) [78]. Subsequent preclinical and early phase clinical trials established that blockage of CTLA4 or PD-1 would potentiate anti-tumor T cell activity [79]. The approval of checkpoint inhibitors, including human monoclonal antibody ipilimumab that blocks CTLA-4 and nivolumab and pembrolizumab that blocks PD-1 thereby stimulating antitumor T cell response, changed the landscape of immunotherapy. The two large phase III randomized trials comparing ipilimumab against standard of care in previously treated (NCT00094653/MDX010-20) and treatment-naive (NCT00324155/CA184-024) metastatic melanoma patients showed significant improvement in overall survival with ipilimumab, and thereby established ipilimumab as the new standard of care [80, 81]. The landmark study MDX010-20 was a 3-arm randomized trial with 676 patients, comparing ipilimumab plus gp100 vaccine, ipilimumab alone, and gp100 alone, and included 77 (11%) patients with stable MBMs not requiring steroids. The median survival was significantly improved in both arms receiving ipilimumab [80]. Similar benefits were seen in patients with or without brain metastases, with hazard ratios for death in patients with brain metastases 0.70 (95% CI 0.41–1.20) for 46 patients receiving ipilimumab plus gp100 vaccine and 0.76 (0.38–1.54) for 15 patients given ipilimumab alone.

A multi-institutional phase 2 study (NCT00623766) assessed the role of ipilimumab in 72 patients with MBMs, of which 51 individuals (cohort A) were neurologically asymptomatic and steroid free, and 21 patients (cohort B) were symptomatic and on stable doses of steroids. The study showed similar proportion of patients achieving overall response rate for intracranial (24% and 10%) and extracranial (27% and 5%) disease sites in cohorts A and B, respectively [82]. Global and CNS immune-related responses were higher in asymptomatic patients who did not require steroids. Median survival was 7.0 months in asymptomatic (cohort A) versus 3.7 months in symptomatic (cohort B) patients [82]. Although immune therapies have poor penetration through the intact blood–brain barrier, studies showed that activated T cells can pass through BBB, and thus immune therapies that stimulate T cell responses may be effective against MBMs [83].

A single-arm phase 2 trial (NIBIT-M1) investigated combination of ipilimumab plus fotemustine in 86 patients with metastatic melanoma, including 20 patients with asymptomatic brain metastases. A 3-year follow-up analysis showed median OS of 12.7 and 12.9 months in patients with MBM and for entire cohort, respectively [84, 85]. Ongoing phase III NIBIT-M2 trial (NCT02460068) is evaluating contribution of fotemustine in a randomized 3-arm study comparing fotemustine alone, fotemustine plus ipilimumab, or ipilimumab plus nivolumab in patients with asymptomatic MBM [86].

Pembrolizumab, a PD-1 inhibitor, has shown 22–26% durable response rates in untreated MBMs (5–20 mm), with an acceptable safety profile, in a recent phase II trial. In this study, brain metastasis and systemic responses were

concordant, with median progression-free and overall survival of 2 and 17 months, respectively, which was similar to patients without brain metastasis treated with anti-PD1 agents [87, 88•].

A phase II study (CheckMate 204, NCT02320058) investigated the combination of nivolumab and ipilimumab in 94 patients with no neurological symptoms and ≥1 measurable, non-irradiated MBM(s) measuring 0.5–3.0 cm. With median follow-up of 14.0 months, the intracranial response was 57%, including 26% complete response rates, which was concordant with extracranial activity. Treatment-related grade 3 or 4 adverse events were reported in 55% of the patients, including one death from immune-related myocarditis [89•]. A recent update of CheckMate 204 evaluated patients with no neurologic symptoms or steroid Rx (asymptomatic; cohort A) and those with neurologic symptoms, whether or not they were receiving steroid Rx (symptomatic; cohort B). With median follow-up of 20.6 months, the intracranial clinical benefit rate, i.e., proportion of patients with complete response + partial response + stable disease ≥ 6 months, in Cohort A was 58.4%. In cohort B, with a median follow-up of 5.2 months, intracranial clinical benefit rate was 22.2% [90]. A multicenter, open-label, randomized phase II Anti-PD1 Brain Collaboration trial (NCT02374242) investigated combination nivolumab plus ipilimumab (cohort A, *n*=36) versus nivolumab alone (cohort B, *n*=27) in patients with asymptomatic MBMs with no prior local radiotherapy and symptomatic patients (cohort C, *n*=16), which showed intracranial response rate of 46% in cohort A, 20% in cohort B, and 6% in cohort C. Intracranial complete responses occurred in 17% of patients in combination cohort A. Treatment-related grade 3/4 adverse events occurred in 54% patients in combination cohort A, and 16% in cohort B, and 26%, and 5% of patients, respectively, discontinued due to an AE [91]. Current evidence from phase II studies as summarized above showed that combination immunotherapy with ipilimumab and nivolumab demonstrated durable intracranial response for patients with asymptomatic MBM, but poor response was evident in symptomatic MBM patients following combination immunotherapy. Further studies are warranted to confirm response and elucidate resistance mechanism with these treatment strategies for patients with asymptomatic MBM. Additional investigation will also be needed to improve therapy for patients with symptomatic MBM (Tables 1 and 2).

Combination of SRS with targeted therapy/immunotherapy

SRS delivers high ablative radiation dose leading to cell apoptosis and might have a synergistic immunomodulatory effect when combined with immunotherapy. To date, there have been several retrospective studies that explored safety and efficacy of concurrent or sequential SRS with targeted therapy or immunotherapy showing excellent local control rates and safety profile. However, prospective data are lacking. In a study reviewing 77 MBM patients, combining ipilimumab with SRS was associated with significant improvement of median overall survival (OS) from 4 · 9 months to 21 · 3 months and 2-year overall survival from 19 · 7% to 47 · 2% compared with SRS alone [92]. Ahmed et al. [93] reviewed 314 MBM patients treated with SRS within 3 months of anti-PD-1, anti-CTLA-4, BRAF/MEK inhibitors, or conventional chemotherapy. Treatment with anti-PD-1, anti-CTLA-4, or BRAF/MEKi significantly improved OS when compared with conventional chemotherapy. Local MBM control rate

Table 1. Summary of pertinent clinical studies evaluating systemic and radiation therapies for melanoma brain metastasis

Author	Study design/No. of patients (MBMs)	Patient population/cohorts	Systemic treatment	Local therapy	Intracranial response (%)	Overall survival	Median brain PFS (months)
Targeted therapy							
Long et al. [67] (2012)	BREAK-MB Phase II Prospective	Asymptomatic Cohort A (*n*=89): no prior local therapy Cohort B (*n*=83): prior local therapy	Dabrafenib (150 mg twice a day until disease progression, death, or unacceptable adverse events)	–	Cohort A: 39·2 Cohort B: 30·8	>31 weeks (median)	>16 weeks
Davies et al. [72••] (2017)	COMBI-MB Phase II Prospective	Cohort A (*n*=76): BRAFV600-E, asymptomatic, no prior local treatment	Dabrafenib + trametinib	–	Cohort A: 58	Cohort A: 10.8 months (median)	Cohort A: 5.6
		Cohort B(*n*=16): BRAFV600-E, asymptomatic + prior local treatment			Cohort B: 56	Cohort B: 24.3	Cohort B: 7.2
		Cohort C (*n*=16): BRAF V600D/K /R, asymptomatic			Cohort C: 44	Cohort C: 10.1	Cohort C: 4.2
		Cohort D (*n*=17): BRAF V600D/E/K /R, asymptomatic			Cohort D: 59	Cohort D: 11.5	Cohort D: 5.5
Immunotherapy							
Margolin et al. [82] (2012)	Phase II	Cohort A: asymptomatic, no steroids	Ipilimumab		Cohort A: 16	Cohort A: 7.0	Cohort A: 2.7
		Cohort B: symptomatic, on stable doses of steroids			Cohort B: 5	Cohort B: 3.7	Cohort B: 1.3
Di Giacomo et al. [84] (2015)	NIBIT-M1 Phase II	No MBM (*N*=86) Asymptomatic MBMs (*N*=20)	Ipilimumab + fotemustine		40	12.7 months (median)	3 months (brain)
Goldberg et al. [88•] (2016)	Phase II	*N*=18/36 (MBMs) Asymptomatic, untreated	Pembrolizumab		22	Median not reached (median FU 11.6 months)	Not reported
Tawbi et al. [89•] (2018)	CheckMate204 Phase II	Asymptomatic, non-irradiated, 0.5–3.0 cm *N*=94 patients	Nivolumab + ipilimumab		57	1 year, 81.5%	9-month PFS, 59.5%

Table 1. (Continued)

Author	Study design/No. of patients (MBMs)	Patient population/cohorts	Systemic treatment	Local therapy	Intracranial response (%)	Overall survival	Median brain PFS (months)
Tawbi et al. [90] (2019)	CheckMate204	Cohort A: asymptomatic Cohort B: symptomatic/ on steroids	Nivolumab + ipilimumab		58.4 22.2	–	–
RT + concurrent immunotherapy/ targeted therapy (retrospective data only)							
Ahmed et al. [93] (2016)	Retrospective 96 (314 MBMs)	Asymptomatic	IMT (Anti-PD1/anti-CTLA4): nivolumab/ pembrolizumab, ipilimumab TT (BRAFi/MEKi): dabrafenib/ trametinib, vemurafenib Chemotherapy: carboplatin + paclitaxel	SRS Single fraction LINAC based	1-year MBM LCR: 83% 1-year DICR Anti-PD1; 38% Anti-CTLA4: 21% BRAF/MEKi: 20% BRAFi: 8% Chemo: 5%	1-year OS: 66% (anti-PD1), 50% (anti-CTLA-4), 75% (BRAF/ MEKi), 15% (chemo)	Median PFS: 3.4 months 1-year PFS: 41% (antiPD-1), 27% (anti-CTLA-4), 39% (BRAF/MEKi), 5% (chemo)
Knisely et al. [92] (2012)	Retrospective	77 patients	SRS alone SRS + ipilimumab	SRS Single fraction Gamma knife		Median OS: 4.9 months (No Ipi), 21.3 months (Ipi) 2-year OS: 19.7% (no Ipi), 47.2% (Ipi)	Salvage WBRT No Ipi: 40% SRS + Ipi: 28%
Acharya et al. [95] (2017)	Retrospective 72 (233 MBMs)	Asymptomatic	IMT (anti-PD1/anti-CTLA4): nivolumab/ pembrolizumab, ipilimumab TT (BRAFi/MEKi): dabrafenib/ trametinib, vemurafenib	SRS: single fraction Gamma Knife	1-year LCR SRS only: 66% SRS + IMT: 85% SRS + TT: 72% 1-year DICR SRS: 11.5% SRS + IMT: 60% SRS + TT: 10%	1-year OS SRS: 31% SRS + IMT: 58%	
Hecht et al. [97] (2018)	Retrospective 155 patients	–	BRAF inhibitor (vemurafenib, dabrafenib)	WBRT or SRS	–	1-year OS RT alone: 9.8 months	Median PFS – 4.2 months

Table 1. (Continued)

Author	Study design/No. of patients (MBMs)	Patient population/cohorts	Systemic treatment	Local therapy	Intracranial response (%)	Overall survival	Median brain PFS (months)
						RT + BRAFi: 12.6 months	
SRS + WBRT (not melanoma specific)							
Brown et al. [48••] (2016)	NCCTGN0574 (Alliance) Phase III *n*=213	Asymptomatic 1–3 BM	–	SRS + WBRT	ICR: 93.7% (3 months), 84.6 (1 year)	7.4 months	Cognitive decline (3 months): 91.7%
				SRS alone	ICR: 75.3% (3 months) 50.5% (1 year)	10.4 months (NS)	63.5%
Chang et al. [47] (2009)	Phase III *n*=86	Asymptomatic 1–3 BM		SRS + WBRT	1-year ICR: 73% 1-year LCR:100% 1-year DICR:73%	Median: 5.7 months 1-year OS: 21%	Cognitive decline (4 months): 96%[a]
				SRS alone	1-year ICR: 27% 1-year LCR:67% 1-year DICR:45%	Median:15.5 months 1-year OS: 63%	24%
Kocher et al. [45] (2011)	EORTC Phase III *n*=359	Asymptomatic 1–3 BM	–	SRS + WBRT	19% (LCR) 33 (DICR)	10.9 months	
				WBRT alone	31% (LCR, *p*=0.04) 28 (DICR, *p*=0.02)	10.7 months (NS)	
Sneed et al. [46] (2002)	Multi-institutional Retrospective *n*=569			SRS + WBRT SRS alone	Not reported	15.2 months 14 months (NS)	
Brown et al. [54] (2017)	NCCTG N107C/ CEC·3 Phase III *n*=194	Single resected BM <5.0 cm	–	WBRT	6-month surgical bed control: 87.1%	11.6 months	6-month cognitive decline: 85%
				Single-fraction SRS	80.4% ($p<0.0007$)	12.2 months (NS)	52%

**SRS*, stereotactic radiosurgery; *IMT*, immunotherapy; *TT*, targeted therapy; *ICR*, intracranial control rate (local + distant intracranial control); *LCR*, local control rates; *DICR*, distant intracranial control rates; *LINAC*, linear accelerator; *WBRT*, whole brain radiotherapy; *RT*, radiotherapy

[a]Trial closed prematurely due to high probability of neurocognitive decline in SRS + WBRT arm

at 12 months was 83%, with no significant differences among the groups. The risk of radionecrosis is reported to be higher in at least one retrospective study suggesting that approximately 10% of patients given ipilimumab in combination with focal radiotherapy or WBRT might be at risk, with a peak incidence around 12–15 months after radiation [94]. Further investigation is warranted.

Acharya et al. [95] investigated SRS within 3 months of immunotherapy or targeted therapy in 72 patients with 233 MBMs. One-year local control for SRS, SRS + immunotherapy, and SRS + targeted therapy were 66%, 85%, and 72%, respectively (p=.04). One-year distant intracranial control rates for SRS, SRS + immunotherapy, and SRS + targeted therapy were 11.5%, 60%, and 10%, respectively (p<.001). This study suggested SRS + immunotherapy was associated with a significant reduction in distant intracranial failure compared with SRS alone or SRS + targeted therapy.

There are little data regarding the timing of targeted therapy dosage relative to SRS, but oncologists commonly withhold targeted therapy for 3–5 days surrounding SRS treatment. Improved brain tumor control and OS were seen in concurrent or post-SRS BRAF/MEK inhibitors, suggesting perturbation of BBB by SRS leading to increased intracranial delivery of these drugs [93, 95, 96]. However, concurrent vemurafenib or dabrafenib and SRS have been reported to increase risk for radiation necrosis and grade≥3 adverse events, especially skin toxicities, and this should be monitored [97–99].

Activation of an anti-tumor immune response after radiotherapy-induced cell death can lead to regression of tumors distant from the irradiated region (known as the abscopal effect). Several studies have reported abscopal effects when radiotherapy is combined with anti-CTLA-4 inhibitors [100]. However, abscopal effect is unpredictable, and its effect for MBMs is largely unknown.

The combination strategy of systemic therapies and SRS needs to be investigated prospectively to assess the optimal sequence of radiation and systemic therapy, radiation (and systemic therapy) dose and radiation fractionation, and risks including radionecrosis. Until then, based on observational non-randomized data, SRS concurrently or sequentially with immunotherapy is well tolerated; a washout period of 3–5 days is usually recommended when combined with targeted therapy [99].

Conclusions

For patients with melanoma brain metastases, treatment decision has become more individualized. A multidisciplinary approach involving medical oncologists, radiation oncologists, and neurosurgery to derive a personalized treatment plan based on prognostic groups, molecular classification, and number and size of brain metastasis can promise possibility of long-term intracranial control. For patients with a good prognosis, the focus is on effectively managing brain metastases while minimizing neurological toxicity and maintaining the quality of life. Surgery should be considered in symptomatic and large MBMs, while SRS considered in 1–4 lesions, and now also being explored for up to 15 brain metastases for improved local control. The role of WBRT is shrinking but yet to be re-defined, given its neurocognitive side effects, except for patients with diffuse brain involvement as a palliative measure. Immunotherapy has become the cornerstone of management for metastatic melanoma. For patients with

Table 2. Ongoing clinical trials of melanoma brain metastasis

Study	Therapy	*N*	Study title	Primary endpoint	Expected completion
Targeted therapy					
NCT02537600 (CONVERCE)	Vemurafenib + cobimetinib	43	Evaluation of Cobimetinib + Vemurafenib Combination Treatment in Patients with Brain Metastasis BRAFV600 Mutated Cutaneous Melanoma	Intracranial response	2020
NCT03911869 (POLARIS)	Encorafenib + binimetinib	100	An Open-Label, Randomized, Multicenter Trial of Encorafenib + Binimetinib Evaluating a Standard-dose and a High-dose Regimen in Patients with BRAFV600-mutant Melanoma Brain Metastasis.	Safety, brain metastasis response rate	2023
Immunotherapy					
NCT03175432	Bevacizumab + atezolizumab vs Bevacizumab + atezolizumab + cobimetinib	60	Phase II Study of BEvacizumab (Avastin) in Combination with Atezolizumab or Atezolizumab (Tencentriq) and Cobimetinib (Cotellic) in Patients with Untreated Melanoma Brain Metastases (TACo-BEAT-MBM)	Safety, intracranial response rate	2021
NCT03728465	Ipilimumab + nivolumab	68	An Open Label Phase II Study to Evaluate Safety and Efficacy of Combined Treatment with Ipilimumab and Nivolumab in Patients with Four and More Symptomatic Brain Metastases of Melanoma	Intracranial control rate	2024
NCT02681549	Pembrolizumab + bevacizumab	53	A Phase 2 Trial of Pembrolizumab Plus Bevacizumab in Patients with Metastatic Melanoma or Non-small Cell Lung	brain metastasis response rate	2024

Table 2. (Continued)

Study	Therapy	*N*	Study title	Primary endpoint	Expected completion
			Cancer with Untreated Brain Metastases		
SRS/WBRT					
NCT04114981	Single-fraction SRS vs fractionated SRS	208	Phase III Trial of Post-Surgical Single Fraction SRS Compared with Fractionated SRS for Resected Metastatic Brain Disease	Surgical bed recurrence-free survival	2025
NCT01644591	SRS	49	A Phase II Trial to Determine Local Control and Neurocognitive Preservation After Initial Treatment with Stereotactic Radiosurgery (SRS) for Patients with >3 Melanoma Brain Metastases	Time to progression, time to neurocognitive failure	2020
NCT03340129	SRS + ipilimumab + nivolumab vs. Ipi/Nivo alone	218	A Phase II, Open Label, Randomized, Controlled Trial of Ipilimumab and Nivolumab With Concurrent Intracranial Stereotactic Radiotherapy Versus Ipilimumab and Nivolumab Alone in Patients with Melanoma Brain Metastases.	Neurological specific cause of death, intracranial response rate	2024
NCT04074096	SRS + binimetinib + encorafenib vs. Bini/Enco alone	150	Phase 2, Randomised Trial Testing the Addition of SRS to Binimetinib and Encorafenib in Comparison with Binimetinib and Encorafenib alone in Patients with BRAFV600 + Melanoma with Brain Metastasis (BECOME-MB)	Intracranial PFS	2026
NCT02716948	SRS + nivolumab	90	A Pilot Study of Stereotactic Radiosurgery Combined with Nivolumab in Patients	Safety, local control rate	2021

Table 2. (Continued)

Study	Therapy	*N*	Study title	Primary endpoint	Expected completion
			with Newly Diagnosed Melanoma Metastases in the Brain and Spine		
NCT02858869	Pembrolizumab + SRS (6 Gy×5, 9 Gy×3, 18–21 Gy×1)	30	Pilot Study of Pembrolizumab and SRS for Patients with Melanoma or Non-Small Cell Lung Cancer Brain Metastases	Dose limiting CNS toxicities	2021
NCT03075072	WBRT (30 Gy/10 fractions) vs SRS (1–5 fractions)	196	Whole Brain Radiation vs SRS in Patients with 5–20 Brain Metastases: A Phase III, Randomized Clinical Trial	Quality of life, neurologic survival	2022
NCT03550391	WBRT (30 Gy/10 fractions) vs SRS (18–22 Gy/1 fractions)	206	A Phase III Trial of SRS Compared with Hippocampal-Avoidant WBRT Plus Memantine for 5–15 Brain Metastases	Overall survival, neurocognitive PFS	2022

asymptomatic MBMs, ipilimumab and nivolumab have shown excellent intracranial response based on results of recent trials including CheckMate 204. For patients with BRAF-mutant melanoma, BRAF/MEK-targeted agents can be considered. Combination of systemic therapy with SRS seems safe and effective based on retrospective data; potential benefits and risks should be evaluated prospectively. Given increasingly complex treatment options, patients with melanoma brain metastases should ideally be evaluated in a multidisciplinary setting for optimal treatment approach and encouraged to participate in clinical trials.

Compliance with Ethical Standards

Conflict of interest

Anupam Rishi declares that he has no conflict of interest. Hsiang-Hsuan Michael Yu declares that he has no conflict of interest.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86. https://doi.org/10.1002/ijc.29210.
2. Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Eheman C, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst. 2011;103(9):714–36. https://doi.org/10.1093/jnci/djr077.
3. Davies MA, Liu P, McIntyre S, Kim KB, Papadopoulos N, Hwu WJ, et al. Prognostic factors for survival in melanoma patients with brain metastases. Cancer. 2011;117(8):1687–96. https://doi.org/10.1002/cncr.25634.
4. 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. https://doi.org/10.3171/jns.1998.88.1.0011.
5. Sloot S, Chen YA, Zhao X, Weber JL, Benedict JJ, Mule JJ, 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. https://doi.org/10.1002/cncr.30946.
6. Frinton E, Tong D, Tan J, Read G, Kumar V, Kennedy S, et al. Metastatic melanoma: prognostic factors and survival in patients with brain metastases. J Neuro-Oncol. 2017;135(3):507–12. https://doi.org/10.1007/s11060-017-2591-9.
7. Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. Nat Rev Cancer. 2009;9(4):274–84. https://doi.org/10.1038/nrc2622.
8. Izraely S, Klein A, Sagi-Assif O, Meshel T, Tsarfaty G, Hoon DS, et al. Chemokine-chemokine receptor axes in melanoma brain metastasis. Immunol Lett. 2010;130(1–2):107–14. https://doi.org/10.1016/j.imlet.2009.12.003.
9. Voura EB, Ramjeesingh RA, Montgomery AM, Siu CH. Involvement of integrin alpha(v)beta(3) and cell adhesion molecule L1 in transendothelial migration of melanoma cells. Mol Biol Cell. 2001;12(9):2699–710. https://doi.org/10.1091/mbc.12.9.2699.
10. Kircher DA, Silvis MR, Cho JH, Holmen SL. Melanoma brain metastasis: mechanisms, models, and medicine. Int J Mol Sci. 2016;17(9). https://doi.org/10.3390/ijms17091468.
11. Johnson DB, Menzies AM, Zimmer L, Eroglu Z, Ye F, Zhao S, et al. Acquired BRAF inhibitor resistance: a multicenter meta-analysis of the spectrum and frequencies, clinical behaviour, and phenotypic associations of resistance mechanisms. Eur J Cancer. 2015;51(18):2792–9. https://doi.org/10.1016/j.ejca.2015.08.022.

12. Bedikian AY, Wei C, Detry M, Kim KB, Papadopoulos NE, Hwu WJ, et al. Predictive factors for the development of brain metastasis in advanced unresectable metastatic melanoma. Am J Clin Oncol. 2011;34(6):603–10. https://doi.org/10.1097/COC.0b013e3181f9456a.
13. Ballo MT, Ross MI, Cormier JN, Myers JN, Lee JE, Gershenwald JE, et al. Combined-modality therapy for patients with regional nodal metastases from melanoma. Int J Radiat Oncol Biol Phys. 2006;64(1):106–13. https://doi.org/10.1016/j.ijrobp.2005.06.030.
14. Huismans AM, Haydu LE, Shannon KF, Quinn MJ, Saw RP, Spillane AJ, et al. Primary melanoma location on the scalp is an important risk factor for brain metastasis: a study of 1,687 patients with cutaneous head and neck melanomas. Ann Surg Oncol. 2014;21(12):3985–91. https://doi.org/10.1245/s10434-014-3829-9.
15. Carlino MS, Haydu LE, Kakavand H, Menzies AM, Hamilton AL, Yu B, et al. Correlation of BRAF and NRAS mutation status with outcome, site of distant metastasis and response to chemotherapy in metastatic melanoma. Br J Cancer. 2014;111(2):292–9. https://doi.org/10.1038/bjc.2014.287.
16. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745–51. https://doi.org/10.1016/s0360-3016(96)00619-0.
17. Morris SL, Low SH, A'Hern RP, Eisen TG, Gore ME, Nutting CM, 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):829–33. https://doi.org/10.1038/sj.bjc.6602018.
18. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70(2):510–4. https://doi.org/10.1016/j.ijrobp.2007.06.074.
19. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. J Clin Oncol. 2012;30(4):419–25. https://doi.org/10.1200/JCO.2011.38.0527.
20.•• Sperduto PW, Jiang W, Brown PD, Braunstein S, Sneed P, Wattson DA, et al. Estimating survival in melanoma patients with brain metastases: an update of the graded prognostic assessment for melanoma using molecular markers (Melanoma-molGPA). Int J Radiat Oncol Biol Phys. 2017;99(4):812–6. https://doi.org/10.1016/j.ijrobp.2017.06.2454
The study updated the DS-GPA specific for MBMs by including molecular markers in a large (n=823) and more contemporary (2006–2015) patient cohort. Melanoma-molGPA scores of 4.0 and 0.0 were associated with the best and worst prognoses. There were 5 significant prognostic factors for survival (age, KPS, extracranial metastases, number of brain metastases, and BRAF status), whereas only KPS and number of brain metastases were included in the original Melanoma-GPA.
21. Carapella CM, Gorgoglione N, Oppido PA. The role of surgical resection in patients with brain metastases. Curr Opin Oncol. 2018;30(6):390–5. https://doi.org/10.1097/CCO.0000000000000484.
22.• Fischer GM, Jalali A, Kircher DA, Lee WC, McQuade JL, Haydu LE, et al. Molecular profiling reveals unique immune and metabolic features of melanoma brain metastases. Cancer Discov. 2019;9(5):628–45. https://doi.org/10.1158/2159-8290.CD-18-1489
Comprehensive molecular profiling on MBMs and patient-matched extracranial metastases showed unique MBM biology as compared with patient-matched extracranial metastases.
23. Fife KM, Colman MH, Stevens GN, Firth IC, Moon D, Shannon KF, et al. Determinants of outcome in melanoma patients with cerebral metastases. J Clin Oncol. 2004;22(7):1293–300. https://doi.org/10.1200/JCO.2004.08.140.
24. 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):111–5. https://doi.org/10.1002/jso.21903.
25. 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;123:117–26. https://doi.org/10.1016/j.clineuro.2014.05.010.
26. Bindal RK, Sawaya R, Leavens ME, Lee JJ. Surgical treatment of multiple brain metastases. J Neurosurg. 1993;79(2):210–6. https://doi.org/10.3171/jns.1993.79.2.0210.
27. Hagen NA, Cirrincione C, Thaler HT, DeAngelis LM. The role of radiation therapy following resection of single brain metastasis from melanoma. Neurology. 1990;40(1):158–60. https://doi.org/10.1212/wnl.40.1.158.
28. Skibber JM, Soong SJ, Austin L, Balch CM, Sawaya RE. Cranial irradiation after surgical excision of brain metastases in melanoma patients. Ann Surg Oncol. 1996;3(2):118–23. https://doi.org/10.1007/bf02305789.
29. 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):401–6. https://doi.org/10.2217/cns.14.40.
30. Susko MS, Garcia MA, Ma L, Nakamura JL, Raleigh DR, Fogh S, et al. Stereotactic radiosurgery to greater than 10 brain metastases: evidence to support the role of radiosurgery for ideal hippocampal sparing in the treatment of multiple brain metastases. World Neurosurg. 2019. https://doi.org/10.1016/j.wneu.2019.11.089.
31. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain

radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro-Oncology. 2013;15(10):1429–37. https://doi.org/10.1093/neuonc/not114.

32. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. Nat Med. 2002;8(9):955–62. https://doi.org/10.1038/nm749.
33. Gondi V, Hermann BP, Mehta MP, Tome 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. 2013;85(2):348–54. https://doi.org/10.1016/j.ijrobp.2012.11.031.
34. Gondi V, Tome WA, Marsh J, Struck A, Ghia A, Turian JV, et al. Estimated risk of perihippocampal disease progression after hippocampal avoidance during whole-brain radiotherapy: safety profile for RTOG 0933. Radiother Oncol. 2010;95(3):327–31. https://doi.org/10.1016/j.radonc.2010.02.030.
35. Gondi V, Pugh SL, Tome WA, Caine C, Corn B, Kanner A, 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):3810–6. https://doi.org/10.1200/JCO.2014.57.2909.
36. Memantine hydrochloride and whole-brain radiotherapy with or without hippocampal avoidance in reducing neurocognitive decline in patients with brain metastases. https://clinicaltrialsgov/ct2/show/NCT02360215.
37.• Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS et al. Hippocampal Avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. J Clin Oncol. 2020;JCO1902767. https://doi.org/10.1200/JCO.19.02767

Phase III trial of WBRT (30 Gy in 10 fractions) plus memantine with or without hippocampal avoidance, showed better preservation of neurocognitive function and patient-reported symptoms, with hippocampal avoidance, while achieving similar intracranial control and survival.

38. Doss LL, Memula N. The radioresponsiveness of melanoma. Int J Radiat Oncol Biol Phys. 1982;8(7):1131–4. https://doi.org/10.1016/0360-3016(82)90060-8.
39. Yamamoto M, Kawabe T, Sato Y, Higuchi Y, Nariai T, Watanabe S, 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. https://doi.org/10.3171/2014.8.GKS141421.
40. Rava P, Leonard K, Sioshansi S, Curran B, Wazer DE, Cosgrove GR, et al. Survival among patients with 10 or more brain metastases treated with stereotactic radiosurgery. J Neurosurg. 2013;119(2):457–62. https://doi.org/10.3171/2013.4.JNS121751.
41. 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 Cancer Netw. 2008;6(5):505–13; quiz 14. https://doi.org/10.6004/jnccn.2008.0038.
42. Liew DN, Kano H, Kondziolka D, Mathieu D, Niranjan A, Flickinger JC, et al. Outcome predictors of Gamma Knife surgery for melanoma brain metastases. Clinical article J Neurosurg. 2011;114(3):769–79. https://doi.org/10.3171/2010.5.JNS1014.
43. 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 Neuro-Oncol. 2008;87(3):299–307. https://doi.org/10.1007/s11060-007-9510-4.
44. Rades D, Bohlen G, Pluemer A, Veninga T, Hanssens P, Dunst J, 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):2515–21. https://doi.org/10.1002/cncr.22729.
45. Kocher M, Soffietti R, Abacioglu U, Villa S, Fauchon F, Baumert BG, 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):134–41. https://doi.org/10.1200/JCO.2010.30.1655.
46. Sneed PK, Suh JH, Goetsch SJ, Sanghavi SN, Chappell R, Buatti JM, 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):519–26. https://doi.org/10.1016/s0360-3016(02)02770-0.
47. Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, 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):1037–44. https://doi.org/10.1016/S1470-2045(09)70263-3.
48.•• Brown PD, Jaeckle K, Ballman KV, Farace E, Cerhan JH, Anderson SK, 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):401–9. https://doi.org/10.1001/jama.2016.9839

The landmark Alliance trial showed lesser cognitive deterioration with SRS alone as compared with WBRT, with similar overall survival. This study abloshed the practice of combined SRS + WBRT, and WBRT is now mostly reserved for diffuse MBMs.

49. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, et al. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90-05. Int J Radiat Oncol Biol Phys. 2000;47(2):291–8. https://doi.org/10.1016/s0360-3016(99)00507-6.

50. Jeong WJ, Park JH, Lee EJ, Kim JH, Kim CJ, Cho YH. Efficacy and safety of fractionated stereotactic radiosurgery for large brain metastases. J Korean Neurosurg Soc. 2015;58(3):217–24. https://doi.org/10.3340/jkns.2015.58.3.217.
51. Burton S, Amankulor N, Engh J, Flickinger J. Fractionated stereotactic radiosurgery for large brain metastases. https://clinicaltrialsgov/ct2/show/NCT02054689. 2019.
52. Soltys SG, Adler JR, Lipani JD, Jackson PS, Choi CY, Puataweepong P, et al. Stereotactic radiosurgery of the postoperative resection cavity for brain metastases. Int J Radiat Oncol Biol Phys. 2008;70(1):187–93. https://doi.org/10.1016/j.ijrobp.2007.06.068.
53. Minniti G, Esposito V, Clarke E, Scaringi C, Lanzetta G, Salvati M, et al. Multidose stereotactic radiosurgery (9 Gy x 3) of the postoperative resection cavity for treatment of large brain metastases. Int J Radiat Oncol Biol Phys. 2013;86(4):623–9. https://doi.org/10.1016/j.ijrobp.2013.03.037.
54. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC.3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1049–60. https://doi.org/10.1016/S1470-2045(17)30441-2.
55. ClinicalTrials.gov. Single fraction stereotactic radiosurgery compared with fractionated stereotactic radiosurgery in treating patients with resected metastatic brain disease. https://clinicaltrialsgov/ct2/show/NCT04114981.(12 Jan 2020, date last accessed).
56. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen W, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18(1):158–66. https://doi.org/10.1200/JCO.2000.18.1.158.
57. Serrone L, Zeuli M, Sega FM, Cognetti F. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res. 2000;19(1):21–34.
58. Wiernik PH, Einzig AI. Taxol in malignant melanoma. J Natl Cancer Inst Monogr. 1993;15:185–7.
59. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010;363(9):809–19. https://doi.org/10.1056/NEJMoa1002011.
60. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239–46. https://doi.org/10.1200/JCO.2010.32.4327.
61. Mittapalli RK, Vaidhyanathan S, Dudek AZ, Elmquist WF. Mechanisms limiting distribution of the threonine-protein kinase B-RaF(V600E) inhibitor dabrafenib to the brain: implications for the treatment of melanoma brain metastases. J Pharmacol Exp Ther. 2013;344(3):655–64. https://doi.org/10.1124/jpet.112.201475.
62. Gerstner ER, Fine RL. Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol. 2007;25(16):2306–12. https://doi.org/10.1200/JCO.2006.10.0677.
63. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012;366(8):707–14. https://doi.org/10.1056/NEJMoa1112302.
64. McArthur GA, Maio M, Arance A, Nathan P, Blank C, Avril MF, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol. 2017;28(3):634–41. https://doi.org/10.1093/annonc/mdw641.
65. Harding JJ, Catalanotti F, Munhoz RR, Cheng DT, Yaqubie A, Kelly N, et al. A retrospective evaluation of vemurafenib as treatment for BRAF-mutant melanoma brain metastases. Oncologist. 2015;20(7):789–97. https://doi.org/10.1634/theoncologist.2014-0012.
66. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet. 2012;379(9829):1893–901. https://doi.org/10.1016/S0140-6736(12)60398-5.
67. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, 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):1087–95. https://doi.org/10.1016/S1470-2045(12)70431-X.
68. Azer MW, Menzies AM, Haydu LE, Kefford RF, Long GV. Patterns of response and progression in patients with BRAF-mutant melanoma metastatic to the brain who were treated with dabrafenib. Cancer. 2014;120(4):530–6. https://doi.org/10.1002/cncr.28445.
69. Poulikakos PI, Persaud Y, Janakiraman M, Kong X, Ng C, Moriceau G, et al. RAF inhibitor resistance is mediated by dimerization of aberrantly spliced BRAF(V600E). Nature. 2011;480(7377):387–90. https://doi.org/10.1038/nature10662.
70. Wagle N, Emery C, Berger MF, Davis MJ, Sawyer A, Pochanard P, et al. Dissecting therapeutic resistance to RAF inhibition in melanoma by tumor genomic profiling. J Clin Oncol. 2011;29(22):3085–96. https://doi.org/10.1200/JCO.2010.33.2312.
71. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444–51. https://doi.org/10.1016/S0140-6736(15)60898-4.

72.•• Davies MA, Saiag P, Robert C, Grob JJ, Flaherty KT, Arance A, 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):863–73. https://doi.org/10.1016/S1470-2045(17)30429-1
COMBI-MB is a phase II clinical trial, which showed intracranial response rates between 44% and 59% with dabrafenib and trametinib. The study established this combination for MBMs, and along with COMBI-AD study (NCT01682083) led to FDA approval of this combination.
73. Greger JG, Eastman SD, Zhang V, Bleam MR, Hughes AM, Smitheman KN, et al. Combinations of BRAF, MEK, and PI3K/mTOR inhibitors overcome acquired resistance to the BRAF inhibitor GSK2118436 dabrafenib, mediated by NRAS or MEK mutations. Mol Cancer Ther. 2012;11(4):909–20. https://doi.org/10.1158/1535-7163.MCT-11-0989.
74. Kalialis LV, Drzewiecki KT, Klyver H. Spontaneous regression of metastases from melanoma: review of the literature. Melanoma Res. 2009;19(5):275–82. https://doi.org/10.1097/CMR.0b013e32832eabd5.
75. Kaufman HL, Wong MK, Daniels GA, McDermott DF, Aung S, Lowder JN, et al. The use of registries to improve cancer treatment: a national database for patients treated with interleukin-2 (IL-2). J Pers Med. 2014;4(1):52–64. https://doi.org/10.3390/jpm4010052.
76. Guirguis LM, Yang JC, White DE, Steinberg SM, Liewehr DJ, Rosenberg SA, et al. Safety and efficacy of high-dose interleukin-2 therapy in patients with brain metastases. J Immunother. 2002;25(1):82–7. https://doi.org/10.1097/00002371-200201000-00009.
77. Hong JJ, Rosenberg SA, Dudley ME, Yang JC, White DE, Butman JA, et al. Successful treatment of melanoma brain metastases with adoptive cell therapy. Clin Cancer Res. 2010;16(19):4892–8. https://doi.org/10.1158/1078-0432.CCR-10-1507.
78. Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol. 2007;19(7):813–24. https://doi.org/10.1093/intimm/dxm057.
79. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol. 2010;28(19):3167–75. https://doi.org/10.1200/JCO.2009.26.7609.
80. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23. https://doi.org/10.1056/NEJMoa1003466.
81. Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015;33(10):1191–6. https://doi.org/10.1200/JCO.2014.56.6018.
82. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012;13(5):459–65. https://doi.org/10.1016/S1470-2045(12)70090-6.
83. Wilson EH, Weninger W, Hunter CA. Trafficking of immune cells in the central nervous system. J Clin Invest. 2010;120(5):1368–79. https://doi.org/10.1172/JCI41911.
84. Di Giacomo AM, Ascierto PA, Queirolo P, Pilla L, Ridolfi R, Santinami M, 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. https://doi.org/10.1093/annonc/mdu577.
85. Di Giacomo AM, Ascierto PA, Pilla L, Santinami M, Ferrucci PF, Giannarelli D, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol. 2012;13(9):879–86. https://doi.org/10.1016/S1470-2045(12)70324-8.
86. ClinicalTrials.gov. A study of fotemustine (FTM) vs FTM and ipilimumab (IPI) or IPI and nivolumab in melanoma brain metastasis (NIBITM2). https://clinicaltrialsgov/ct2/show/NCT02460068. (12 Dec 2019, date last accessed).
87. Kluger HM, Chiang V, Mahajan A, Zito CR, Sznol M, Tran T, 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. https://doi.org/10.1200/JCO.18.00204.
88.• Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2016;17(7):976–83. https://doi.org/10.1016/S1470-2045(16)30053-5
This phase II study was initial and seminal evidence to show durable response rate of 22–26% with pembrolizumab in untreated MBMs with an acceptable safety profile. Important to note in this study, brain metastasis and systemic responses were concordant.
89.• Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med. 2018;379(8):722–30. https://doi.org/10.1056/NEJMoa1805453
Landmark phase II study CheckMate 204 investigated combination of nivolumab + ipilimumab in asymptomatic non-irradiated MBM, which showed intracranial response of 57%, including 26% complete response rates, which was concordant with extracranial activity. Although relatively small non-randomized study, reported data is pertinent to clinical practice with given the high intracranial and extracranial response

rate, rapid time to response, and manageable side-effect profile.

90. Tawbi HA-H, Forsyth PAJ, Hodi FS. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). J Clin Oncol. 2019;37:9501. https://doi.org/10.1200/JCO.2019.37.15_suppl.9501.
91. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81. https://doi.org/10.1016/S1470-2045(18)30139-6.
92. Knisely JP, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VL. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J Neurosurg. 2012;117(2):227–33. https://doi.org/10.3171/2012.5.JNS111929.
93. Ahmed KA, Abuodeh YA, Echevarria MI, Arrington JA, Stallworth DG, Hogue C, 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):2288–94. https://doi.org/10.1093/annonc/mdw417.
94. Du Four S, Hong A, Chan M, Charakidis M, Duerinck J, Wilgenhof S, et al. Symptomatic histologically proven necrosis of brain following stereotactic radiation and Ipilimumab in six lesions in four melanoma patients. Case Rep Oncol Med. 2014;2014:417913. https://doi.org/10.1155/2014/417913.
95. Acharya S, Mahmood M, Mullen D, Yang D, Tsien CI, Huang J, 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):572–80. https://doi.org/10.1016/j.adro.2017.07.003.
96. Mastorakos P, Xu Z, Yu J, Hess J, Qian J, Chatrath A, et al. BRAF V600 mutation and BRAF kinase inhibitors in conjunction with stereotactic radiosurgery for intracranial melanoma metastases: a multicenter retrospective study. Neurosurgery. 2019;84(4):868–80. https://doi.org/10.1093/neuros/nyy203.
97. Hecht M, Meier F, Zimmer L, Polat B, Loquai C, Weishaupt C, et al. Clinical outcome of concomitant vs interrupted BRAF inhibitor therapy during radiotherapy in melanoma patients. Br J Cancer. 2018;118(6):785–92. https://doi.org/10.1038/bjc.2017.489.
98. Hecht M, Zimmer L, Loquai C, Weishaupt C, Gutzmer R, Schuster B, et al. Radiosensitization by BRAF inhibitor therapy-mechanism and frequency of toxicity in melanoma patients. Ann Oncol. 2015;26(6):1238–44. https://doi.org/10.1093/annonc/mdv139.
99. Kroeze SG, Fritz C, Hoyer M, Lo SS, Ricardi U, Sahgal A, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. Cancer Treat Rev. 2017;53:25–37. https://doi.org/10.1016/j.ctrv.2016.11.013.
100. 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. https://doi.org/10.1186/s13045-018-0647-8.

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