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Melanoma Brain Metastases: An Unmet Challenge in the Era of Active Therapy

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Abstract

Metastatic disease to the brain is a frequent manifestation of melanoma and is associated with significant morbidity, mortality, and poor prognosis. Surgery and stereotactic radiosurgery provide local control but less frequently affect the overall outcome of melanoma brain metastases (MBM). The role of systemic therapies for active brain lesions has been largely under-investigated and those patients are excluded from the vast majority of clinical trials. The advent of active systemic therapy has revolutionized the care of melanoma patients but this benefit has not been systematically translated into intracranial activity. In this article, we review the biology and clinical outcomes of patients with MBM, the evidence supporting the use of radiation, surgery, and systemic therapy in MBM. Prospective studies that included patients with active MBM have shown clinical intracranial activity that parallels systemic activity and support the inclusion of patients with active MBM in clinical trials involving novel agents and combination therapies.

Keywords

Melanoma; Brain Metastases; Systemic Therapy; Targeted Therapy; Immunotherapy; Dabrafenib; Ipilimumab; Stereotactic Radiosurgery; Prognosis; Biology; Local control; BRAF; MEK

INTRODUCTION

In 2013, there will be an estimated 76,690 new melanoma patients and 9480 melanoma-related deaths in the USA.¹ Population studies demonstrate cutaneous melanoma as the third most common cause of brain metastasis (MBM) development reflecting its distinctive neurotropism.^{2,3} Approximately 40–50% of Stage IV melanoma patients eventually develop clinical manifestations of MBM.^{4,5} The prevalence is likely higher as autopsy series have reported 55% to 75% of melanoma patients have MBM.^{2,4,6}

Although outcomes vary for patients with melanoma MBM, overall prognosis remains poor. The overall survival reflects the effects of therapy on both intracranial and extracranial disease at the time of presentation and may not be entirely representative of intracranial

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Conflict of Interest

John Kirkwood has been a consultant for GSK, Novartis, Merck, MBS, Celgene and Vical and has received a grant from Prometheus. Hussein A. Tawbi and Vikram Gorantla declare no conflict of interest.

Human and Animal Rights and Informed Consent

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disease control. The minority of patients who show extended survival (> 3 years) are generally characterized by the presence of locally treated solitary MBM without known extracranial disease.^{7,8} Conversely, patients with multiple MBM and extensive visceral disease exhibit particularly poor survival outcomes which can be as short as 1 to 2 months for symptomatic disease.^{9,10} Even with early diagnosis and aggressive local therapy, MBM is the cause of death in nearly 95% of patients.^{6,7,11} The bleak outcomes of melanoma MBM have not been mitigated over the past 3 decades and while the last 4 years have brought tremendous promise for patients with metastatic melanoma, this has not previously translated into improved outcomes for MBM, since these patients have been systematically excluded from most clinical trials of systemic therapy.¹⁰

Clinical Predictors of Melanoma Brain Metastases

Several large, albeit retrospective, series have examined the role of clinical and molecular features that could serve as biomarkers for the development of MBM. Factors that have been shown to increase the risk for development of central nervous system (CNS) metastasis in melanoma patients included male sex, thickness or ulceration of the primary lesion, site in the head and neck, mucosal, or acral lentiginous tumors, and nodular primary lesions.^{7,12} These markers of high risk disease predict more generally for visceral metastatic involvement.¹³ On multivariate analysis, factors that retained independent predictive significance were site of origin in the head and neck, and ulceration of the primary lesion.¹²

The correlation between BRAF or NRAS mutations and development of MBM remains under investigation. Genetic screens of melanoma MBM for BRAF mutation status have shown almost equal distributions of BRAF wild-type and mutant genotypes (48–55.3% mutant).^{14,15} Colombino et al.¹⁵ showed an interesting discordance in terms of mutation status between primary melanomas and MBM qualified by small numbers (n=4, 20% discordance). Development of MBM overall was noted to be similar among stage IIIC and IV patients with BRAF mutant vs. wild-type (WT) (34% vs. 39 %, p=0.453) and also in regard to brain as first site of metastases (10% vs. 15% for WT). Presence of BRAF mutation did not appear to impact the time to first distant metastases.¹⁶ In a recent retrospective review¹⁷ however, patients whose tumors harbor BRAF and NRAS mutations were noted to be more likely to have CNS disease at the time of distant metastases. NRAS mutation was associated with a poor prognosis compared to WT in this study. NRAS has also been noted to be associated with thicker tumors and higher mitotic rates.¹⁸

Prognosis of patients with new MBM depends upon primary tumor characteristics and clinical variables. Heterogeneity of disease characteristics and clinical presentation present a challenge in risk stratifying patients and predicting prognosis. Three factors: age, Karnofsky Performance Score (KPS), and status of extracranial disease were used by the Radiation Therapy Oncology Group (RTOG) to group patients with similar prognosis for comparison across clinical trials. Pooled data from 3 consecutive prospective randomized control trials (RCT) – approximately 1200 patients treated with only whole brain radiation therapy (WBRT) – were used to develop a recursive partition analysis (RPA) and generate risk categories for patients. Class 1 patients (age < 65 years, well controlled primary, and KPS 70) survive the longest – median survival of 7.1 months, class 3 (KPS < 70, uncontrolled primary) had the poorest outcomes – median survival of 2.3 months and class 2 patients, which comprised the majority (all others with KPS 70) had a median survival of 4.2 months.¹⁹ This model was validated in only 1 study of melanoma patients receiving WBRT with survival rates of 151, 71, and 21 days in class 1, 2, and 3, respectively.²⁰ In another study, RPA was shown to give significant differences by univariate but not multivariate analyses.²¹ Primary tumor characteristics that retained significance on univariate analysis include ulceration, NRAS status, mitotic index, pretreatment serum lactate dehydrogenase, and S100B levels. Clinical variables that were significant on univariate analysis included the

presence of multiple MBM (> 3), RPA class, neurological symptoms including number of symptoms, age (> 65 years), poor response to therapy, presence of leptomeningeal disease, advanced extracranial metastasis or uncontrolled visceral disease, poor Karnosky performance status (KPS), shorter timing of development of metastases with respect to presentation, and whether MBM developed after systemic therapy.^{5,12,21–23} On multivariate analysis in various studies, ulceration, NRAS mutation, extent of extracranial disease, neurological symptoms, age and number of MBM^{5,10,12,16,21,24} demonstrated significance.

Biology of Melanoma Brain Metastases

The blood brain barrier (BBB) and neurotropism are biological keys to improved future therapeutic measures and to understanding the resistance of MBM to previous therapies. Multiple theories have been put forward to explain the development of metastases. The ‘seed and soil’ hypothesis by Stephen Paget in the late 19th century explained the steps of tumor cell “seed” entering the blood stream and traveling to distant sites based on an inherent affinity for a site “soil” to enable the development of metastases. James Ewing proposed that metastases tend to occur in vascular organs, which would favor embolization and occur purely by circulatory and physical mechanisms. According to the metastatic cascade theory, development of metastases is a sequential concatenated process with primary tumor cells spreading to lymph nodes, proliferating there and then spreading from the node to distant sites. This hypothesis is no longer tenable in its simplest form, as ongoing research suggests that the signals that promote lymphatic and hematogenous dissemination differ, and that the metastatic potential of cell lines derived from lymph node metastases and MBM reveal varied metastatic potential.^{25,26} Another concept has been that there is co-migration of tumor cells (“seeds”) with stromal components such as fibroblasts (“soil”). Cell lines that generate MBM have been developed to better understand mechanisms of MBM^{27,28} in mouse models.

The development of MBM requires the tumor to penetrate the BBB, manipulating the brain microenvironment for survival and successful evasion of host defenses. The BBB presents a physical barrier between systemic circulation and cerebrospinal fluid (CSF). The makeup including tight junctions, pericytes, and astrocytes allows only small hydrophilic molecules to pass through. Large molecules require to be actively transported via receptor-mediated transcytosis. Also the BBB expresses multi-drug resistance proteins and efflux pumps. Reduced shear force at vascular branch points in the cerebral hemispheres²⁹ allow for tumor cells to attach to not only endothelial cells but also leukocytes and platelets via selectins, integrins, and chemokines.^{30–32} Binding to integrins allows for attachment to endothelial surfaces and triggers down-stream signaling and upregulation of vascular endothelial growth factor (VEGF).³³ VEGF upregulation prepares the tumor cell to co-opt pre-existing brain vasculature but also decreases the integrity of the endothelial cell layer, allowing for transvascular migration of tumor cells.³⁴ BBB permeability is further increased by various mechanisms including VEGF, COX2³⁵ and extracellular matrix-degradative enzymes directed at BBB extracellular matrix (ECM)³⁶ such as matrix-metalloproteinase-1³⁷ and heparanase.^{29,38} After malignant cells have crossed the BBB, adaptation in the brain microenvironment by inducing processes such as VEGF pathways and cytokine binding allow for tumor growth and invasion. Upregulation of various VEGF-A isoforms promotes neovascularization and angiogenesis.^{39,40} Melanoma shows a propensity to co-opt existing vasculature which allows tumor sizes up to 3 mm without additional blood supply, mimicking dormancy. Cytokine release and the inflammatory response that follows astrocytic and microglial response counter-intuitively stimulate tumor development through direct interactions and paracrine signaling.⁴¹ Astrocytes seem to exert pro-neoplastic effects and support brain invasion.^{42,43} Some of the mechanisms include overexpression of the ECM-degrading enzyme heparanase⁴³ and cytokine production leading to paracrine

signaling. Astrocytes have also been shown to reduce tumor cell apoptosis when treated with various chemotherapeutic drugs e.g cisplatin, and 5-FU, in cultures.⁴² Microglia- the main immune effectors of the CNS, *in vitro* seem to exert tumoricidal effects through release of nitric oxide⁴⁴ but *in vivo* seem to support tumor proliferation by altering the microenvironment.⁴⁵ Paracrine signaling via neurotrophins such as nerve growth factor (NGF) exert an anti-apoptotic, pro-mitotic and chemotactic effect to allow for neurogenesis. Neurotrophin receptors p75(NTR) and TrkC⁴⁶ expressed on melanoma cells take advantage of these qualities to stimulate and sustain their growth and migration via induction of heparanase and/or cytoskeletal rearrangements.⁴⁷

CLINICAL PRESENTATION

Expanding tumor mass effects lead to increased intracranial pressure, impingement on critical neural pathways, impaired cerebrospinal fluid drainage leading to neurological symptoms including headaches, seizures and focal deficits related to the affected regions of the brain. Given the propensity of this vascular tumor to hemorrhage, sudden onset of symptoms often heralds life threatening intracranial bleeding. Asymptomatic metastases are detected due to surveillance imaging of patients with risk factors (e.g. extensive visceral disease) but more often during screening for clinical trials in which CNS evaluation is mandated, or for established therapies where imaging of the brain is done as a precaution, such as interleukin-2 (IL-2). Melanoma is prone to involve the brain with multiple lesions, a majority supratentorial in location.⁴⁸ Supratentorial lesions > 1cm and most hemorrhagic lesions can be detected by computed tomography (CT) of the brain, performed with and without contrast enhancement. Magnetic resonance imaging (MRI) with and without gadolinium remains the imaging study of choice given increased sensitivity in detecting smaller lesions, ability to evaluate posterior fossa, and detect leptomeningeal disease.⁴⁹

TREATMENT MODALITIES OF MELANOMA BRAIN METASTASES

Melanoma tends to be refractory to both radiotherapy and traditional chemotherapy. This biology portends a poorer prognosis when patients develop MBM, potentially compounded by the role that the BBB has been presumed to serve as a barrier to systemic therapies. Performance status, symptoms, extent and control of visceral disease, along with the size, location and number of MBM, as well as tumor mutation status affect decisions regarding management of intracranial disease and also may be associated with outcomes vis-à-vis survival. The goals of therapy have historically been palliative, with treatment modalities such as whole brain radiation therapy (WBRT), surgery, and stereotactic radiosurgery (SRS) being useful for local tumor control, while chemotherapy, immunotherapy, and biologics aimed at systemic control have been fraught with uncertainty. Supportive measures including corticosteroids for cerebral edema-related symptoms, anticonvulsants, and analgesia are critical in the management of these patients especially in the acute setting.^{50,51}

Options for local management of MBM are surgery, SRS, and less often over the past decade, WBRT. Local control of tumor volume is achieved most rapidly by surgery and SRS whereas WBRT delivers lower dosages of radiotherapy to the whole brain, including unaffected areas, and gives suboptimal control of disease, even when limited in size and number of lesions. The advantages of surgery are its rapid relief of the sequelae of masses on surrounding tissues and structures, and evacuation of bleeds (common in melanoma) as well as the procurement of tissue for diagnosis and ancillary studies. Although the size of the tumor does not limit surgery, it is dependent on the accessibility of the site of tumor involvement. In patients with multiple lesions, dual approach using surgery to manage the symptomatic lesion and SRS for the remainder is used.

Surgery

In comparison to best supportive care, surgical metastectomy has been shown to prolong survival in multiple large retrospective series.^{7,10,52} Outcomes were also improved when compared to WBRT.¹⁰ Patients with solitary MBM, with high KPS and minimal or controlled extracranial disease derived benefit from surgery + WBRT vs. WBRT^{53–55} (Table 1). A retrospective, single institution cohort study demonstrated that patients with good performance status, with multiple MBM (<4) who underwent resection of all MBM had median survival of 14 months which was comparable to patients with single lesion metastectomy.⁵⁶ This study also showed that patients with incomplete resections derived no benefit and median survival was lower at 6 months. Patients who underwent resection of multiple MBM seemed to derive overall survival benefit^{7,10,21,22,24}, this is however a select population.

Stereotactic Radiosurgery

Melanoma patients represent a subset in most prospective RCT looking at SRS alone or in combination with WBRT. Melanoma is considered relatively refractory to conventional fractionated dose regimens. Cell lines grown *in vitro* have been shown to have an ability to repair radiation damage.^{57,58} This finding may not be applicable given that SRS is delivered as an ablative dose, not fractionated. SRS has emerged as a major alternative to surgery in patients with RPA Class I, size < 3cm, deep tumor locations, minimal symptoms, absence of edema and midline shift or hydrocephalus and in those with contraindications to surgery including extensive systemic disease.⁵⁹ Review of outcomes for 333 melanoma patients with MBM who underwent gamma knife radiosurgery showed local control (complete or partial regression or lesion stability) in 94.3% of lesions and in 78.4% of patients.⁶⁰ The median survival after SRS was 5.6 months. Although not statistically significant, two studies seemed to show SRS as a viable alternative to surgery (Table 1).^{61,62} Addition of SRS to WBRT may offer improved overall survival in selected patients (Table 1).^{63,64} Retrospective series of melanoma cases has shown that SRS is an effective treatment modality.^{65,66}

Whole Brain Radiation Therapy

In patients where surgery and SRS are contraindicated because of the numbers of tumor sites, location, size and comorbidities including extent of systemic disease, WBRT is an option for palliation of symptoms including headaches, seizures, and altered mentation.⁶⁷ There is little evidence that WBRT alters the survival of patients with MBM. Sampson et al.⁷ showed median survival of 4 months for 180 patients treated with WBRT only. Another retrospective analysis of 102 patients treated only with WBRT showed overall median survival of 51 days with median survival of 151, 71 and 21 days for RPA class 1, 2 and 3, respectively ($P < 0.001$).²⁰ Recent data⁶⁸ showed higher dose (40Gy in 20 fractions vs. 30 Gy in 10 fractions) had longer median OS (median 5.6 months vs. 3.1 months, $p = 0.003$). The role of “adjuvant” WBRT after surgical resection remains controversial given the radioresistant nature of melanoma and neurocognitive deficits associated with treatment. Theoretical benefits of WBRT include reduced rates of local relapse and reduced emergence of new parenchymal disease in the organ. In one of the largest retrospective analysis of melanoma patients¹⁰, patients treated with surgery and WBRT had a median survival of 8.9 months ($n = 158$), 3.4 months for patients treated with WBRT only ($n = 236$) and 2.1 months for best supportive care ($n = 210$). Benefit was derived from surgery in multivariate analysis detecting no survival benefit to adding WBRT. Similar findings were reported by Sampson et al.⁷ in patients with MBM. However, Buchsbaum et al.²³ in a retrospective trial involving 74 patients with MBM suggested survival benefit of adding WBRT to local therapy – median survival of 8.8 months vs. 4.8 months with local therapy only vs. 2.3 to 3.6 months with WBRT only ($p < 0.01$). The addition of WBRT to SRS appears to improve local control, decrease intracranial relapse and need for salvage therapy but does not appear to

convey survival benefit in patients with melanoma MBM.^{69–71} Given neurocognitive toxicities associated with WBRT and no clear evidence of a survival benefit, the use of WBRT in the adjuvant setting remains controversial, with observation and salvage therapy considered a viable option. Multiple prospective RCT including NCCTG N0574 evaluating addition of WBRT to local treatment modalities are currently underway.⁷²

Systemic Therapy

Standard chemotherapy has shown limited responses in treatment of melanoma brain metastases. The impermeability of the BBB to some chemotherapeutic agents, the role of efflux pumps, and paracrine signaling by astrocytes which serve an anti-apoptotic mediator upon tumor cells may contribute to the challenges of MBM treatment. Possible disadvantages of biologics include polar surface area, lipophilicity, and large molecular weight.⁷³ Given these issues and the generally poor overall outcomes, melanoma patients with MBM are consistently excluded from clinical trials.

Chemotherapy—Single agent Dacarbazine (DTIC) is approved by the Food and Drug Administration (FDA) for treatment of metastatic melanoma. Response rates (8%–20%) and duration of response (4–6 months) in extracranial disease varies. DTIC has poor CNS penetration exhibiting poor activity against MBM.⁷⁴ Although no RCT was conducted to compare DTIC to best supportive care, DTIC has been used as a reference for comparison of newer agents in clinical trials. Chemotherapeutic agents that have shown promise include temozolomide (TMZ), fotemustine, and lomustine. These agents have the ability to readily cross the BBB.^{75,76} TMZ, an oral analogue of DTIC was evaluated in multiple phase II trials as a single agent and in combination with WBRT (Table 2) showing benefit.^{77–79} TMZ did not seem to offer preventative effect against MBM in prospective phase III trial.⁸⁰ Dose dense TMZ schedules also failed to show benefit with a median OS of 3.3 months.⁸¹ Fotemustine, a highly lipophilic drug, demonstrated overall response rate (ORR) of 24% in a phase II trial⁸² however this did not carry over to a phase III trial comparing it to DTIC – cerebral responses of 5.9% vs 0%. Drug approval has not been granted by the FDA for use in the United States given concern for delayed thrombocytopenia and leukopenia. A phase I/II study⁸³ - lomustine in combination with TMZ did not show activity with a median survival of two months.

Immunotherapy—The CNS is generally considered to be an immunologically privileged site. The BBB prevents conventional circulation of lymphocytes and antibodies. Microglia, macrophages and dendritic cells serve as antigen presenting cells in the brain. However several studies have shown that activated T cells can cross the BBB^{84,85} leading to the hypotheses that T cell responses would be effective.⁸⁶ Immunotherapy agents including ipilimumab, IL-2, vaccines and adoptive cell therapy have shown benefit in metastatic melanoma. Patients with symptomatic or untreated MBM were excluded from clinical studies involving these agents given slow onset of action and associated toxicities including hemorrhage, seizures and edema. Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte associated antigen 4 (CTLA-4). CTLA-4 is an inhibitory immune checkpoint which down regulates T-cell proliferation. Blocking CTLA-4 leads to T cell proliferation and associated immunological response including IL-2 production and cytotoxic activity. Ipilimumab has been shown to improve overall survival in phase III studies and is FDA approved since 2011 for the treatment of metastatic melanoma. Ipilimumab improved overall survival when compared with a gp100 vaccine in second line therapy⁸⁷, but a subgroup analysis of patients with MBM remains pending. In a phase II study of patients with untreated MBM, ipilimumab at 10mg/kg showed disease control in 16% of patients⁸⁸ (Table 2) and median duration of response of an impressive 15 months in patients that were asymptomatic and off steroids, however in a parallel cohort for patients who remained on

steroid therapy, no responses were observed and the study did not proceed to its second stage. This suggests that the benefit of ipilimumab is similar in MBM to patients with extracranial disease potentially after local control of MBM and completion of steroid therapy.⁸⁸ Combination ipilimumab and fotemustine showed intracranial disease control in 50% of patients with MBM (n=10, 5 with stable or partial response and 5 with complete response).⁸⁹ Clinical trials of IL-2 based therapy have generally excluded patients with MBM given concern for IL-2 mediated capillary leak induced edema causing increased intracranial pressure and thrombocytopenia causing hemorrhage.⁹⁰ Retrospective studies support the use of IL-2 or IL-2 based biochemotherapy in those with treated MBM.⁹⁰⁻⁹² Guirguis et al.⁹⁰ reviewed safety and efficacy of high dose IL-2 in 1069 metastatic melanoma and renal cell patients. A subset of 37 patients with untreated MBM demonstrated a 5.6% response rate for both intracranial and extracranial metastatic sites.⁹⁰ Another approach has been to extract lymphocytes from a patient with metastatic disease, induce ex vivo activation and expansion of these lymphocytes and their reinfusion back to the patient - Adoptive cell therapy. A study conducted at the National Cancer Institute, which looked at autologous tumor-infiltrating lymphocytes (TIL) with host lymphodepletion and IL-2 showed objective response rates of 50% to 70% in patients with refractory metastatic melanoma.⁹³ Complete MBM response was obtained in 41% of patients receiving TIL vs. 22% of patients who received T-cell receptor-transduced lymphocytes in this study. Autologous dendritic cells loaded with patient specific melanoma antigens have also shown promise in phase II trials⁹⁴.

Targeted Therapy—Better understanding of cell signaling pathways have lead to the design of targeted therapies and shown benefit in advanced melanoma. The MAPK (RAS-RAF-MEK-ERK) pathway has proven a target rich environment given association of RAS and RAF mutations with melanoma. BRAF inhibitor therapy in metastatic melanoma patients with BRAF V600 mutations continues to be explored given high clinical response rates seen with vemurafenib⁹⁵ and dabrafenib (GSK2118436).⁹⁶ Dabrafenib showed activity in patients with untreated MBM which harbored V600 BRAF-mutant patients in a phase I/II clinical trial with varying response in patients with MBM.⁹⁷ One third of these patients had more than 3 MBM. Nine patients had a reduction in the size of the MBM and 4 had a complete response in the brain. A recently concluded phase II trial evaluated dabrafenib in patients with BRAF mutation V600E or V600K with untreated or progressive MBM demonstrated unequivocal clinical activity. Patients with V600E mutation and previously untreated MBM showed approximately 38% overall response versus 31% for patients with previously treated but progressive disease. The 6-months overall survival was an impressive 61%.⁹⁸ Preclinical evidence had indicated that dabrafenib and its active metabolites have limited BBB penetration which is intriguing given the impressive clinical responses. Based on those findings, a translational study is ongoing examining CSF and tumor tissue excised from patients with untreated BRAF-mutated melanoma MBM after 1–2 weeks of therapy with dabrafenib.

MEK inhibition with MEK162 was evaluated in patients harboring NRAS or BRAF mutation in a phase 2 study.⁹⁹ In patients with treated and stable MBM MEK162 showed promising activity in NRAS mutated patients. Two NRAS mutated patients showed decrease in size of target lesions, two other showed stable disease, but no studies to date have been conducted with MEK inhibitors in patients with NRAS mutated active melanoma MBM.

CONCLUSION

Therapeutic progress in the treatment of melanoma in recent years has primarily occurred in patients without MBM or in those patients with MBM whose MBM were treated with local approaches (surgery/radiation) and under control. This is somewhat paradoxical as this

population (melanoma with MBM) that unfortunately represents over 50% of patients with metastatic disease and the subpopulation that has the worst prognosis. Single agent BRAF inhibitor dabrafenib has been proven safe to administer in patients with BRAF-mutated melanoma and active MBM and has activity that parallels extracranial activity⁹⁸. Similarly, single agent ipilimumab has been proven safe and at least as effective intracranially.⁸⁸ In patients without MBM, the combination of dabrafenib and trametinib (a selective MEK1/2 inhibitor) has improved response rates and progression-free survival duration as compared to single agent therapy with dabrafenib. Also, there is ample preclinical rationale to combine BRAF inhibitor/MEK inhibitor with immunotherapy such as ipilimumab. Those findings should be expanded and combinatorial therapy should be brought to this population to assess the efficacy as well as safety of targeted therapy in combination with immunotherapy. In addition to the expected biological synergy of those 2 approaches, the ability of targeted agents to forestall the progression of melanoma metastases may prove most relevant logistically in this population where rapid progression leads to imminent death and lack of ability of immune therapy to reap its full benefit.

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Table 1

RCT evaluating Local treatment modalities of brain metastases irrespective of histology.

Study	RPA	# of lesions	Treatment arms	Median Overall survival
Patchell et al. (n= 48) ⁵³	I	1	Surgery + WBRT (n=25, m=2)	10 months (p=0.01)
			WBRT (n=23, m=1)	3.3 months
Vecht et al. (n=63) ⁵⁴	I	1	Surgery + WBRT	12 months (p=0.04)
			WBRT	7 months
Mintz et al. (n=84) ⁵⁵	I–III	1	Surgery + WBRT (n=41, m=NA)	5.6 months (p=0.24)
			WBRT (n=43, m=NA)	6.3 months
Muacevic et al. (n=64) ^{±61}	I	1	Surgery + WBRT (n=33, m=5)	9.5 months (p=0.8)
			SRS (n=31, m=4)	10.3 months
Andrews et al. (n=333) ⁶³	I, II	1–3	SRS+WBRT (n=164, m=7)	6.5 months (p=0.039)
			WBRT (n=167, m=7)	4.9 months
Kondziolka et al. (n=27) ^{*64}	I, II	2–4	SRS+WBRT (n=13, m=NA)	11 months (p=0.22)
			WBRT (n=14, m=NA)	7.5 months
Aoyama¹⁰⁰ et al. (n=132)	I, II	1–4	SRS+WBRT (n=65, m=NA)	7.5 months (p=0.42)
			SRS (n=67, m=NA)	8 months

Abbreviations: n, number of patients.; m, number of patients with melanoma; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; RCT, randomized control trial; NA, not available;

[±] Stopped prematurely given poor accrual.

^{*} Stopped after 60% accrual given benefit seen with local control in combined arm.

Table 2

Systemic therapy trials including patients with brain metastases.

Study	Study Design	Treatment Arms	Overall Intracranial Response (CR +PR)	Median OS
Agarwala et al.⁷⁷ n= 155	Phase II, open label.	TMZ n=117 (No prior systemic chemotherapy)	8 (7%)	3.5 months
		TMZ n=34 (Prior systemic chemotherapy)	1 (2%)	2.2 months
Hofman et al.⁷⁹ n=35	Open label.	TMZ n=13	1 (7%)	5 months
		TMZ +SRS n=12	1 (8%)	9 months
		TMZ + WBRT n=10	1 (10%)	7 months
Margolin et al.⁷⁸ n=31	Phase II, single arm.	TMZ + WBRT	3 (9.6%)	6 months
Di Giacomo et al.⁸⁹ n=20	Phase II, open label, single arm.	Ipi + fotemustine	8 (40%)	13.4 months
Margolin et al.⁸⁸ n=72	Phase II, open label.	Ipi n=51 (Asymptomatic)	8 (16%)	7 months
		Ipi n=21 (Symptomatic on steroids)	0 (0%)	3.7 months
Falchook et al.⁹⁷ n=10	Phase I, dose escalation.	Dabrafenib	9 (80%)	NR
Long et al.⁹⁸ n=172 BRAF mutation positive	Phase II, open label.	Dabrafenib Cohort A, n=89 (No previous local treatment)	30 (33%)	V600E 8.1 months V600K 4 months
		Dabrafenib Cohort B, n=83 (Previous local treatment)	24 (29%)	V600E 8 months V600K 5.2 months

Abbreviations: n, number of patients with brain metastases; TMZ, temozolomide; Ipi, Ipilimumab; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; CR, complete response; PR, partial response; SD, stable disease; PFS, progression free survival; OS, overall survival; NR, not reported.