

Management of melanoma brain metastases (mbm)



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Abstract:

Melanoma is the third most common cause of brain metastases, after lung and breast cancer. Common clinical manifestations include headache, neurologic deficits, cognitive impairment and seizures. The management of melanoma brain metastases (MBM) can be broadly divided into symptom control and therapeutic strategies. Supportive treatment includes corticosteroids to reduce peritumoral edema, antiepileptics for seizure control and medications to preserve cognitive function. Until recently the therapeutic strategies focused on local treatment including surgery, whole brain radiation therapy (WBRT), and stereotactic radiation (SRS). Historically, systemic therapy has had limited utility. Immunotherapeutic drugs like anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD1) and agents targeting BRAF- MEK pathway have revolutionized the systemic treatment of MBM. Recent clinical trials with these agents have shown activity against MBM and increasingly being used in clinical practice. In this article, we will discuss epidemiology, biology of MBM and the role of surgery, WBRT, SRS in this patient population. An overview of the currently available systemic therapeutic agents that includes immunotherapy and targeted tyrosine kinase inhibitors (TKIs) and a practical multidisciplinary management algorithm to guide the practicing oncologist will be outlined.

1. Introduction:

Recent advances in the management of advanced melanoma have resulted in improved 5-year survival rates, however, MBM remain a significant cause of morbidity and mortality. Approximately 20% of metastatic melanoma

patients have brain metastases at diagnosis. Overall about 50% of stage IV melanoma patients will develop symptomatic brain metastases (1-3).

Cerebral hemispheres are the site of 80% of brain lesions from melanoma followed by the cerebellum (15%) and brainstem (5%)(4). Common clinical manifestations include headache, neurologic deficits, cognitive impairment and seizures. Until recently, patients with MBM had a dismal prognosis with a median overall survival (OS) of 6 months (5).

The management of MBM can be broadly divided into supportive management and therapeutic strategies. Supportive treatment includes steroids to reduce peritumoral edema, antiepileptics for seizure control and medications to preserve cognitive function. Traditionally, therapeutic strategies focused on local treatment including surgery, WBRT, and SRS. Historically, systemic therapy has had limited utility in the management of MBM. However, the treatment paradigm has changed considerably with the advent of targeted therapy and immunotherapy. Approximately 50% of advanced melanoma patients harbor a *BRAF* mutation and a number of targeted agents for this mutation and downstream pathway have shown promise in the management of metastatic melanoma. Immunotherapeutic agents like anti- CTLA-4 and anti- PD-1 have shown clinical efficacy in MBM and now constitute first line treatment options for metastatic melanoma.

2. Biology of brain metastases:

Until recently MBM were believed to have the highest mutational discordance compared to the primary site (6). However, Chen et al. reported molecular profiling that included hot spot mutations, global mRNA expression patterns, quantitative analysis of protein expression and activation by

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reverse protein array (RPPA) analysis of 16 patients (7). In this study, authors reported complete concordance in mutational profile between intracranial and extracranial sites. Despite these similarities crucial differences in the expression of PI3K/AKT pathway were noted by RPPA. Another study compared the expression of *BRAF* mutation in different sites of metastases in advanced melanoma and showed greater mutational concordance (16/20 patients) in brain compared to other visceral/subcutaneous metastases (8). These studies provide an initial understanding of the molecular characteristics of MBM.

With the advent of immunotherapy, tumor microenvironment and immune infiltration has been a focus of intense research. Brain has been traditionally thought of as an immune privileged organ but recent studies have established the existence of a neuro-immune axis and questioned this belief(9). Our understanding of this unique interplay between the immune system and central nervous system has dramatically evolved over time. Berghoff et al. investigated the expression of PD-1, PD-L1, CD3, CD8, CD45RO, forkhead box protein 3 (FoxP3), CD20, and BRAF V600E by immunohistochemistry in MBM samples (10). Varying degrees of tumor infiltrating lymphocytes (TILs) were reported in this study, 33 out of 43 specimens stained positive for CD3(+) T-lymphocytes, 39 for CD8(+) T-lymphocytes, 32 for CD45RO (+)memory T-lymphocytes, 27 for PD-1(+), 21 for FoxP3(+) T regulatory lymphocytes, and 19 for CD20(+) lymphocytes. Significant tumoral PD-L1 expression (> 5%) was observed in 9 specimens while 22 samples stained positive for PD-L1 suggesting role of immunotherapeutic agents in MBM.

3. Prognostic indices

Although the median OS of MBM is dismal, approximately 5% patients are long term survivors(2). Hence prognostic factors that predict outcomes and can guide the treatment decisions and enrollment in clinical trials are of value. Several large single center series have examined various primary tumor, brain metastases, and patient characteristics predictive of survival (2, 11, 12). Age, performance status, number of brain metastases, extra-cranial metastases, time from primary tumor diagnosis, presence of neurologic symptoms and elevated LDH are factors that determine survival. (13).

Sperduto et al proposed a new disease based scoring index based on 483 newly diagnosed MBM patients from 8 different centers (14). On multivariate analysis, performance status and number of BMs were prognostic for survival in MBM. The outcomes of ds-GPA MBM varied from GPA class I with survival of 3. 4 months to GPA class IV with survival of 13. 2 months.

These prognostic indices have inherent limitations. All of them were evaluated retrospectively, had only overall survival as the end point, did not include molecular and genetic profile of the primary malignancy, and did not take systemic therapy into consideration (15). A large single institutional experience of 366 patients treated to 1, 336 brain metastases has also shed some light on the interplay of important prognostic variables in patients with MBM. In this series, characteristics associated with survival included younger age, lack of extracranial metastases, performance status, and treatment with BRAF inhibitors or immunotherapies. This work specifically highlights the importance of modern outcomes in patients who are eligible for and receive newer targeted therapies. For example, the 12-month survival

estimate for patients treated with BRAF inhibitors was 37% compared to 23% for those patients who did not receive these therapies ($p= 0. 01$). Moreover, the 12-month survival estimate for patients treated with immunotherapies was 47% compared to 22% for those patients who did not receive these therapies ($p= 0. 04$). Clearly, further work is needed to define the impact of mutation, targeted drugs and immunotherapy in the current era.

4. Diagnosis:

The neurologic symptoms associated with brain metastases include headaches, seizures, cranial nerve deficits to motor or sensory deficits. All melanoma patients with neurologic symptoms worrisome for MBM should undergo a gadolinium enhanced magnetic resonance imaging (MRI) of the brain, if no contraindications exist. Guidelines recommend routine MRI of brain with and without gadolinium contrast for patients with stage IV melanoma due to the high prevalence of asymptomatic brain metastases(16). Computed tomography of brain with and without contrast can be used as an alternate imaging.

5. Management:

The options available for management of brain metastases include surgery, WBRT, SRS, systemic therapy and symptom management. The management plan to treat these patients should take into account the overall prognosis, performance status and morbidity associated with the treatment.

5. 1 Management of symptoms:

Supportive care for patients with brain metastases is typically to control the cerebral edema with steroids. Due to minimal mineralocorticoid effect and <https://assignbuster.com/management-of-melanoma-brain-metastases-mbm/>

long half-life, dexamethasone is the steroid of choice, however, other steroids at an equivalent dose can be used and tapered gradually over a two week period(17). A randomized trial in 1990s compared different doses of dexamethasone ranging from 4 mg/day to 16 mg/day and concluded that 4-8 mg/day would provide same degree of clinical improvement in 1 week (18). Routine use of prophylactic anti-epileptics in patients with brain metastases is not recommended(19). When patients have seizures several anti-epileptics are available including phenytoin, carbamazepine, valproic acid and levetiracetam. Non-enzyme inducing agents like levetiracetam are preferred to avoid interactions with systemic agents.

5. 2 Neurosurgical Options:

Surgery has traditionally been used for management of solitary brain metastases, or large symptomatic brain lesions. Multiple retrospective studies have reported improved survival with surgery compared to best supportive care(13, 20-22). Younger patients with good performance status, fairly well-controlled extracranial disease, solitary brain metastasis, lesions in accessible locations and of small size generally have better outcomes with surgery (21, 23). Surgery is usually followed by radiation boost to the surgical bed by either WBRT or SRS, with an intention of sterilizing the surrounding tissues and preventing local recurrence. Two randomized trials comparing adjuvant WBRT to surgery alone have shown improvement in outcomes(24, 25). Patchell et al. evaluated the role of WBRT post-resection of a single brain metastasis compared to surgery alone(25). Postoperative WBRT resulted in a significant reduction in local and distant intracranial failure. However, no difference in the overall survival or time duration of

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functional independence was noted. Similar results were seen in the EORTC 22952-26001 study with decreased 2-year intracranial and resection site recurrence without significant survival benefit. Multiple retrospective reports of post-operative SRS have shown improved patient outcomes however prospective data is awaited (26, 27). Bindal et al. showed benefit of resection in select group with multiple metastases in a retrospective review of 56 patients(28). In practice, surgery plays an important role in debulking or removal of life-threatening lesions. Surgery also provides immediate relief from intracranial hypertension by eliminating the mass effect, and symptomatic hydrocephalus by reestablishing the flow of cerebrospinal fluid (CSF).

5. 3 Whole brain radiation therapy:

Melanoma brain metastases lesions are generally considered radio-resistant compared to other histologies (29). Randomized trials with WBRT have reported survival in the range of 2. 4 to 4. 8 months.(30) The ideal dose and number of fractions, balancing the intracranial control and cognitive decline, has been subject to intense debate. WBRT fraction sizes of ≤ 3 Gy do not lead to significant neuro-cognitive decline. A retrospective study compared higher dose of radiation, 40 Gy in 20 fractions with 30 Gy in 10 fractions(31). The 40 Gy group had overall survival of 5. 6 months compared to 3. 1 months. However most of these trials were not melanoma specific and included patients with all tumor types. Patients who are symptomatic with change in mentation, headaches and seizures but are deemed unfit for surgery or SRS due to large number of metastases, poor performance and uncontrolled extracranial metastases are generally treated with WBRT(32).

5. 4 Stereotactic radiation therapy:

Stereotactic radiation has been increasingly used in the management of MBM in the last two decades. SRS in MBM results in local control rates of 50-75% at 1 year(33-35). SRS is generally limited to lesions smaller than 4 cm in diameter (36). In a retrospective review of 333 patients treated with SRS showed a sustained tumor control rate of 73%(35). The 12-month cumulative incidence of local failure was 14% in another single institution experience of 191 patients treated to 793 MBM. Number of brain metastases that can be treated with SRS has been intensely investigated. SRS for solitary brain metastasis was compared to surgery plus WBRT in a phase III trial that closed prematurely due to poor accrual. The overall survival, freedom from local recurrence and neurological death rates were similar in both groups(37). Several studies have evaluated the role of SRS in patients with 1-3 brain metastases (38, 39). Aoyama et al. compared SRS alone with SRS followed by WBRT in patients with 1-4 brain metastases(38). No difference in neurocognitive function and survival was observed. SRS-alone arm had increased local and distant intracranial failure. A phase III trial compared WBRT followed by SRS to WBRT alone, in 333 patients with 1-3 brain metastases from different histologies that included only 13 MBM patents (40). Performance status at six months improved significantly with addition of SRS to WBRT. SRS for patients with 5-10 brain lesions was evaluated in a multi-institution prospective observational Japanese study of 1194 patients(41). The overall survival, neuro-cognitive function and post SRS complications did not differ for patients with 5-10 brain lesions compared to 2-4 brain lesions(42).

5. Systemic therapy:

Traditional systemic therapy had a limited role in MBM due to challenges of drug delivery in the brain from blood brain barrier (BBB) with its tight junctions and efflux pumps (P-gp and MRP transport proteins) (43). The concept of localized disruption of BBB at the site of brain metastases has been proposed, as demonstrated on MRI by contrast enhancement (44).

1. Chemotherapy:

Chemotherapy agents have not shown good activity in MBM. Dacarbazine which is the approved chemotherapy for metastatic melanoma does not cross the BBB(45). A number of studies evaluated the role of alkylating agents with good BBB penetration such as temozolomide (TMZ), lomustine and fotemustine in MBM patients. In a phase II trial Agarwala et al. enrolled 151 MBM patients with no local radiation therapy for BM to receive TMZ (46). TMZ use showed a modest intracranial response of 6%, median PFS of 4.3-5.2 weeks and median OS of 3.2 months. Two phase II trials of WBRT with TMZ(47, 48); or thalidomide, WBRT with TMZ (49) failed to improve the response rates significantly. Lomustine in combination with TMZ showed modest efficacy in a phase I/II study(50). Intracranial activity of fotemustine was first reported in a phase III trial of fotemustine versus dacarbazine for metastatic melanoma (51). This led to a randomized phase III trial that compared fotemustine plus WBRT to fotemustine alone in MBM (52). The response rates were 7.4% for fotemustine alone and 10% for fotemustine plus WBRT. Fotemustine is not currently approved by FDA for use in MBM due to delayed thrombocytopenia and leukopenia(53).

2. Targeted therapy:

BRAF, *NRAS* and *KIT* are three common, mutually exclusive driver mutations seen in metastatic melanoma (54, 55). Of these three, *BRAF* mutation is the most common mutation seen in approximately 40-50% of patients with advanced melanoma. The presence of *BRAF*, *NRAS* increases the risk of CNS metastases seen in patients with advanced melanoma. Prior studies have reported 24% CNS metastases rate in *BRAF* and 23% CNS metastases incidence in *NRAS* mutant melanoma compared to 12% rate in those who lack these mutations(56). Dabrafenib and vemurafenib target *BRAF*^{V600} mutation and FDA approved for metastatic melanoma.

A phase I trial of dabrafenib in ten patients with untreated asymptomatic brain metastases, intracranial response was seen in 8 patients (four CR, four PR) (57). This impressive 80% response rate prompted the phase II trial of dabrafenib in *BRAF* mutant melanoma brain metastases (BREAK-MB) (58). This multicenter open label study accrued 172 patients' asymptomatic brain metastases with *BRAF*^{V600E} or *BRAF*^{V600K} mutation and one measurable lesion (defined as at least 1 cm in diameter). Cohort A consisted of 89 patients who were radiation naive and cohort B consisted of 83 patients who had failed prior radiation therapy for BM. *BRAF*^{V600E} patients had an intracranial response rate (IRR) of 39% (29/74) in cohort A and 31% (20/65) in cohort B, PFS of 16. 1 weeks in cohort A and 16. 6 weeks in cohort B with OS of 33. 1 weeks in cohort A and 31. 4 weeks in cohort B. *BRAF*^{V600K} patients had a lower IRR of 7%(1/15) in cohort A and 22% (4/18) in cohort B. This trial supports the efficacy of dabrafenib in *BRAF* mutant MBM patients, especially those with *BRAF*^{V600E} mutations with acceptable toxicity.

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In an open label study of 24 non-resectable, untreated MBM patients harboring *BRAF*^{V600} mutation, treatment with vemurafenib resulted in tumor regression of more than 30% (7/19) and partial response was seen in 3 patients. Median PFS and OS was 3.9 and 5.3 months respectively in this study. In a phase II study, 146 *BRAF* mutant MBM patients were treated with vemurafenib (59). The first cohort included 90 patients with untreated BM, the second cohort comprised of 56 patients with previously treated BM. Complete response was noted in 2 patients, with 14 PRs, and a best objective response rate of 18%. In previously untreated MBM, the median intracranial PFS and OS were 3.7 months and 8.9 months respectively. Previously treated MBM had similar PFS and OS of 4.0 months and 9.6 months respectively.

There is no prospective data of safety and efficacy of combination of BRAF inhibitors and radiation therapy. Most reports are retrospective in nature with increased incidence of dermatitis seen in extracranial skin associated with concurrent use of BRAF inhibitors and radiation (60). Rompoti et al. reported five patients with MBM treated with combined radiation and BRAF inhibitor (61). Two patients underwent SRS and three received WBRT. Patients treated with SRS did not experience any skin adverse effects while all three patients treated with WBRT noted grade 1/2 dermatitis. A retrospective analysis evaluated effectiveness of vemurafenib and radiation in *BRAF*^{V600} MBM (62). All of them received vemurafenib, six patients underwent SRS, two received WBRT, one received SRS and WBRT and three underwent surgery and radiation. Thirty-six of the 48 index lesions responded with 23 (48%) CRs and 13 (27%) PRs. Major limitations were the

retrospective nature of the study, small number, and pretreated patients with radiation and systemic therapy including ipilimumab. Several small retrospective case series have reported outcomes of MBM treated with targeted agents and SRS/WBRT (Table-1). A recent study of 19 patients with *BRAF* mutations undergoing SRS and concurrent BRAF directed therapies has shown impressively few local failures (12-month cumulative incidence of 1%). Additional studies of combination therapy are clearly warranted.

3. Immunotherapy:

Melanoma is an immunogenic malignancy (63) with a high mutational burden that results in high number of neo-antigen(64). It has been proposed that the relatively high neo-antigen burden makes this malignancy more susceptible to immunotherapy. However, the brain has traditionally been considered an immunologically privileged site due to the presence of the BBB. Recent studies on the intracranial tumor microenvironment as elucidated above have suggested otherwise, showing CD8 T-cells, CD 20+ cells, T-regulator cells and PD-L1 expression within intracranial tumor(10).

The intracranial activity of interleukin-2 (IL-2, one of the first immune modulatory agents) was reported in two retrospective reviews(65, 66). A response rate of 5.6% was seen in 37 patients with untreated brain metastases within a larger group of 1069 metastatic melanoma and renal cell carcinoma patients treated with high dose IL-2(65). In a second report, two of the 15 brain metastases patients treated with high dose IL-2 showed CR (66). No prospective trials were initiated with high dose IL-2 due to concerns for cerebral edema and neurotoxicity.

Two pathways that have revolutionized the management of advanced melanoma are those involving CTLA-4 and PD-1/PD-L1. The CTLA-4 receptor is expressed exclusively on T-cells and downregulates the interaction between antigen presenting cells and T-cells. Ipilimumab is a fully human monoclonal antibody against the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)(67). The pivotal phase III trial that compared ipilimumab with or without gp 100 peptide vaccine to gp 100 vaccine as a single agent allowed enrollment of patients with asymptomatic and/or previously treated MBM (68). A non-significant trend towards better survival in the MBM subgroup was noted among the patients treated with either ipilimumab alone or ipilimumab plus gp 100 compared to gp 100 alone(69). In an expanded access program (EAP) in Italy, 146 MBM patients received ipilimumab and a global response rate of 12% was seen (70). An American EAP reported a 1-year overall survival rate of 20% among 165 MBM patients treated with ipilimumab (71). Margolin et al. conducted an open label phase II clinical trial of ipilimumab for MBM (72). The trial enrolled 72 patients 51 patients in cohort A (those who were not on steroids for cerebral edema) and cohort B of 21 patients (on treatment with steroids). According to the WHO criteria, the response rate was 18% (9/51) in cohort A compared to 5% (1/21) in cohort B, and by immune-related response criteria the response rate was 25% (12/51) in cohort A and 10% (2/21) in cohort B. The median OS was 7.0 months and 3.7 months in cohort A and cohort B respectively. The study concluded that ipilimumab can be used safely in MBM patients. An Italian phase II trial tested a combination of ipilimumab and fotemustine in patients with advanced melanoma including asymptomatic MBM patients (73). A total of 20 patients (out of 83 patients) had asymptomatic MBM, and among these

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patients the study reported a PFS of 3.0 months and 3-year OS rate of 27.8% (74). A randomized, 3 arm, phase III trial of fotemustine, versus fotemustine plus ipilimumab, versus ipilimumab plus nivolumab (NIBIT-M2) is currently recruiting patients (75). Several retrospective studies have evaluated the safety of combining ipilimumab and radiation therapy (SRS or WBRT), and prospective trial data is forthcoming (76-78).

PD-1 receptors are expressed on several cells including T-cells and antigen presenting cells. Their interaction with PD-L1 ligands on tumor cells leads to T-cell exhaustion and downregulation of tumor-specific immune response(79). Nivolumab and pembrolizumab are two anti-PD-1 antibodies that are currently approved for the management of advanced melanoma, and several others are under evaluation. An open label, single-center, phase II clinical trial is currently enrolling patients with untreated brain metastases from melanoma or non-small cell lung cancer (80). In a published early analysis, a response rate of 22% (4 patients) was reported in a total of 18 MBM patients and the responses were durable. Authors noted a high concordance between systemic and brain metastasis responses. Additionally, 11% (2 patients) had stable disease. Intriguingly all responders lacked a *BRAF* mutation. Relatedly, 4 patients were not evaluable either due to rapid progression necessitating BRAF-targeted therapy (3 patients), or intralesional hemorrhage (1 patient). Toxicities in the MBM cohort included grade 3 transaminitis (1 patient), as well as grade 1-2 seizures (3 patients) and grade 3 cognitive dysfunction (1 patient) from peritumoral edema.

Leptomeningeal disease in melanoma

Leptomeningeal disease (LMD) is a subset of metastatic with extraordinarily poor prognosis and median survival of 8 weeks(81, 82). About 5% of malignant LMD originates from melanoma (Kesari) and up to 23% of melanoma cases develop LMD(1, 83). Primary leptomeningeal melanoma also exists as a separate clinical entity and should be a consideration in the context of a person with multiple congenital melanocytic nevi(84). Diagnosis of LMD is usually made based on the combination of neurologic symptoms along with corresponding leptomeningeal enhancement on MRI. While cytology from cerebrospinal fluid (CSF) is considered to be the gold standard for LMD diagnosis, sensitivity of this testing ranges from 50% to 80%, depending on number of lumbar punctures performed (85). Like with MBM, treatment of LMD with chemotherapy has low response rates(86). The clinical course of LMD is more treacherous in melanoma in other malignancies given the propensity for melanoma LMD to hemorrhage(87). Molecular characterization of melanoma LMD suggests a higher percentage of *BRAF* mutations in comparison to the general melanoma population (68% v 45%), based on a single center melanoma LMD cohort of 60 patients(76). Several case reports have been published highlighting complete and partial responses as well as prolonged ongoing survival beyond 15-18 months with BRAF inhibitors (86). Immunotherapy approaches, including intrathecal IL-2, adoptive cell therapies with tumor infiltrating lymphocytes (TILs) and cytotoxic T-lymphocytes (CTLs), and immune checkpoint inhibitors, have also reported prolonged survival in comparison to historic medians (86). A single center study of 38 patients with melanoma LMD who were treated with intrathecal IL-2 reported a median survival of 9.1 months, and the best 15% of patients reached a median survival over 24 months(88). Ongoing survival

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over 18 months in a melanoma LMD case was reported with WBRT followed by ipilimumab, an immune checkpoint CTLA-4 inhibitor; in this case, treatment with ipililumab resulted in complete radiologic response(89). A phase II trial of combination immunotherapy with ipilimumab and nivolumab, a PD-1 inhibitor, in melanoma LMD has recently opened to accrual(90). In summary, these early data suggest that both targeted therapy and immunotherapy have efficacy in melanoma LMD and can result in durable responses well over a year. Upcoming trials addressing melanoma LMD with newer therapies will likely yield significantly improved survival data over the next decade.

6. Conclusion:

Despite significant recent improvement in the outcomes of patients with melanoma, brain metastases remain a major determinant of mortality and morbidity in melanoma patients, and patients with MBM remain in the worst prognostic category. The vast majority of clinical trials with newer agents exclude patients with MBM, thus data on the effectiveness of new drugs in the context of MBM is still lacking. Understanding the biology of MBM and its clinical response to newer agent and particularly combinations of agents and strategies is crucial to increasing the longevity of the poorest-risk melanoma. Appropriate care of MBM begins with diagnosis. In melanoma, the brain is a common site of metastatic spread, both early and late. It is crucial to begin screening patients for MBM at diagnosis, and NCCN guidelines have recently been updated to reflect this changing diagnostic paradigm. The frequency at which to repeat imaging is still not known.

Several therapeutic options now exist for the treatment of MBM (A proposed algorithm is provided in Figure-1). Surgical resection, radiation therapy, targeted therapy and immunotherapy all show some degree of efficacy with MBM. Even in cases of LMD, perhaps the worst subset of MBM in terms of survival, treatment with targeted therapy and immunotherapy can induce prolonged survivals from historic means. Initial reports involving combinations of these therapies, such as radiotherapy with either targeted therapy or immunotherapy, appear promising, but will need to be systematically studied in cohorts with larger numbers. Equally important will be the parallel investigation of predictive markers in MBM with these therapies and combinations. Thus, whenever possible, patients with a new diagnosis of brain metastases should be enrolled in appropriate clinical trials. If an appropriate clinical trial is unavailable, treatment decisions should be made with input from a multidisciplinary team including radiation oncologists, neurosurgeons, and medical oncologists.