Review Article

Systemic therapies for melanoma brain metastases: which drug for whom and when?

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Abstract: Melanoma brain metastases are common, difficult to treat, and are associated with a poor prognosis. Historically, due to the poor activity of chemotherapeutic agents in melanoma, the management of brain metastases was centred on local treatments such as surgery, stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT) depending on the clinical presentation. New systemic therapies have now evolved; kinase inhibitors targeting BRAF mutated melanoma cells and activating checkpoint inhibitors that activate an immune anti-tumour response, resulting in significantly improved survival and quality of life for patients with metastatic melanoma and these drugs have demonstrated activity in melanoma brain metastases. As the landscape shifts to incorporate these new systemic agents with the available local therapies, further research into using appropriate combinations or sequences of various treatments, especially for active or progressing melanoma brain metastasis, is required. This review will examine the evidence for systemic therapies in patients with active melanoma brain metastasis (untreated or treated and progressed) and highlight active and evolving clinical trials in this challenging field.

Keywords: Melanoma; brain metastases; drug; systemic therapy; BRAF

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Introduction

Metastatic melanoma (stage IIIc unresectable or stage IV) is associated with a poor prognosis, and until recently, a median overall survival (OS) of 6-9 months (1). For patients who develop brain metastasis, the median survival is reduced to 17 to 22 weeks (2,3). The incidence of overt brain metastasis at first presentation is approximately 20% and approximately 50% of stage IV melanoma patients develop brain metastases during the course of their disease (3). The presence of BRAF or NRAS mutations increases the risk of developing brain metastasis at first diagnosis of metastatic disease (4). In addition to reduced life expectancy, patients with symptomatic lesions experience neurocognitive decline and poor quality of life (5). The aim of treatment is to reduce neurological symptoms, minimise cognitive decline and improve survival. Recently, incorporation of such patients into clinical trials assessing newer systemic therapies has provided increased therapeutic options, and raises questions regarding the optimal selection and combinations of treatment modalities for brain metastasis.

Prognostic and predictive factors for brain metastasis in melanoma

Clinicopathological factors predictive of short central nervous system (CNS) metastasis-free interval were M1b/M1c disease, head and neck primaries, superficial spreading/nodular subtypes and elevated baseline serum lactate dehydrogenase (LDH) (6,7). Molecular predictors of brain metastases are emerging and include the association of BRAF, NRAS and PTEN mutations and survival. The presence of a BRAF mutation was predictive of increased response rate to BRAF targeted therapy and was associated with significantly improved survival in comparison with BRAF wild-type patients and hence also of prognostic

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significance (8). There have been inconsistent reports of associations of NRAS mutations with prognosis in melanoma (9). Several studies have reported the NRAS mutations to be significantly associated with poorer prognostic features in the primary (10), shorter melanoma-specific survival from primary diagnosis (10) and poorer survival from stage IV diagnosis (4). The PTEN mutations (loss of expression of tumour suppressor PTEN) are mutually exclusive with NRAS mutations, are associated with BRAF V600 mutations and BRAF/NRAS wild type tumours and are predictive of shorter OS and shorter time to brain metastases (11).

In large retrospective studies of melanoma patients with brain metastases, poor prognostic factors associated with worse survival were >3 parenchymal brain lesions, leptomeningeal disease, brain lesions developing concurrently with extracranial disease or while on systemic therapy for extracranial disease, poor performance status (Karnofsky performance status <70%), elevated pre-treatment LDH levels and Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class III (12-15). Patients with limited intracranial disease treated with neurosurgery or stereotactic radiosurgery (SRS) had better survival in comparison with those with diffuse disease and who received whole brain radiotherapy (WBRT) (16).

Systemic therapies

Until recently, systemic therapy in melanoma brain metastasis was limited to using chemotherapeutic agents after failure of local therapies. This is because melanoma cells are resistant to chemotherapy and response rates in the brain have been poor (17-20). It has been proposed that the lack of activity is due to inadequate penetrance of blood brain barrier and expression of active efflux transporters such as P-glycoprotein and breast cancer resistance protein (BCRP) (21). However, the extracranial activity is also limited with these drugs. The BRAF inhibitors dabrafenib, vemurafenib and the anti-CTLA4 antibody ipilimumab have shown activity in such patients with active (untreated or progressed after previous therapy) melanoma brain metastases in phase 2 studies, with increased response rates and improved survival compared with historic controls (17,22,23). The selection of an appropriate systemic agent depends on the patient's performance status, presence of medical co-morbidities precluding use of a drug, number and size of brain metastases, neurological symptoms and complications, burden of extracranial metastases and tumour mutation status (24,25).

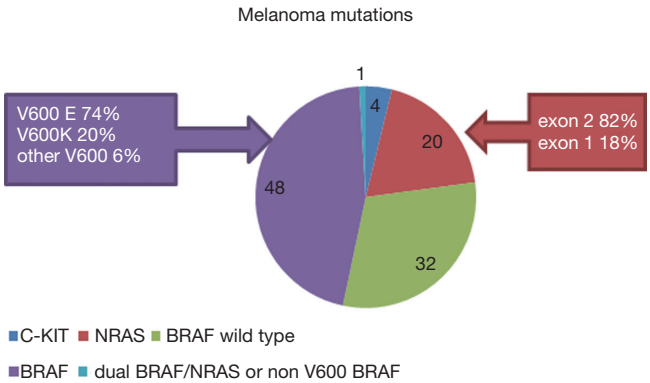

Figure 1 Distribution of mutations in melanoma.

Somatic mutations in melanoma and clinicopathological associations

Melanoma is associated with a high burden of somatic mutations and aberrations (26), the most frequent and well-known mutations are the BRAF and NRAS mutations, occurring in 35-45% and 15-25% of melanoma patients (8,10,27,28), along with the KIT mutation, which occur in 3-4% of western populations with melanoma (27). The BRAF and NRAS mutations are the focus of targeted drug therapy in melanoma.

The serine-threonine kinase BRAF is a component of the RAF-MEK-MAPK pathway [known as the mitogen activated protein kinase (MAPK) pathway] and point mutations in the BRAF gene occur in 33-47% of primary melanoma and 41-55% of metastatic melanomas (8,27,29) (*Figure 1*). The most common BRAF mutation is V600E, occurring in 74-76% of all BRAF mutations (8,27), and is due to the substitution of the amino acid valine with glutamic acid at position 600 of the BRAF protein, resulting in activation of downstream kinases. The BRAF V600K [occurring in 10-20% of BRAF mutations (8,27)] results from substitution of valine with lysine at position 600 of the BRAF protein. Other V600 mutations are rare (6%) (4,8,9). DNA sequencing (using Sanger sequencing, often combined with high resolution melt analysis to increase sensitivity) or pyro-sequencing, immunohistochemistry, as well as PCR based testing platforms are used to detect these mutations in tumour samples with varying sensitivities and specificities (30). The Roche Cobas 4800 is a real-time PCR technique which detects BRAF mutations V600E, V600K,

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V600D, with only high sensitivity and specificity for the BRAF V600E mutations (31). Immunohistochemistry utilises a specific monoclonal antibody (VE1) for detecting BRAF V600E protein in melanoma and is a highly sensitive (97%), specific (98%), rapid and a cost-effective analysis, utilising minimal tissue (32,33). It provides a result at the time of pathological diagnosis and accurately discriminates BRAF V600E mutations from non-V600E mutations. There are many methods of BRAF mutation testing that are approved by country-specific laboratory agencies [e.g., Clinical Laboratory Improvement Amendments (CLIA), USA], and the role for other bodies e.g., the Food and Drug Administration (FDA) is less clear as the treatment landscape for solid tumours is changing with the advent of targeted therapies.

Multiple studies have examined the association of various mutations and general clinicopathological features, in stage IIIc unresectable and stage IV melanoma patients with BRAF V600E mutations. They were younger at the time of diagnosis (median age, 44.7 years), had primary cutaneous melanoma of superficial spreading or nodular histology, originating in the trunk or extremities and lacked evidence of chronic sun damage. Patients with V600K mutation were older (median age, 60 years) and had primaries of head and neck origin. Patients with BRAF mutations had shorter disease free interval from the diagnosis of the primary tumour to the development of metastatic disease (8), however patients with V600E mutations had longer OS from stage IV diagnosis, in comparison with those with V600K mutations (34).

The NRAS mutations are less common in advanced melanoma. The most common NRAS mutations are in exon 2 (82%—Q61R, Q61K, Q61L) and less often in exon 1 (18%) (34). The exon 2 mutations are frequent in cutaneous primaries of the nodular subtype; while the exon 1 mutations are frequently associated with mucosal melanomas (34). Lack of available targeted therapy for this group of patients confers worse outcomes in comparison with BRAF mutated advanced melanoma patients on BRAF inhibitor therapy and this opens up avenues to explore new pharmacotherapies in this patient subgroup.

Mutations activating the receptor tyrosine kinase c-kit are uncommon in cutaneous (chronic sun damage) melanomas (3%), but occur commonly in melanomas arising from mucous membranes and acral skin (20%) (35). Asian patients had a higher incidence of c-kit mutations (10.8%) when compared to Caucasians patients (2-4%) (27,36,37). Although there are multiple other aberrations in melanoma, and other aberrations are gaining increasing importance e.g., NF1 mutations, the BRAF, NRAS and KIT mutations are mutually exclusive (except for approximately 1%), and at this stage remain the focus for the development of targeted drugs.

BRAF inhibitors and combination therapies in BRAF mutated melanoma brain metastases

Both dabrafenib and vemurafenib are potent small molecule reversible ATP-competitive serine threonine kinase inhibitor of BRAF V600E mutated melanoma cells, resulting in inhibition of downstream activated MAPK pathway and has substantial activity in BRAF mutated melanoma brain metastasis. Phase 3 trials of dabrafenib and vemurafenib showed significantly improved response rates, progression free and OS, in comparison to dacarbazine, in BRAF mutated advanced melanoma but excluded patients with active or untreated brain metastasis (38,39).

Activity of dabrafenib in active brain metastasis was demonstrated in a large multicentre, open-label, phase 2 trial which enrolled 172 BRAF V600E, V600K mutated metastatic melanoma patients and at least one measurable brain metastasis (5-40 mm diameter), into cohort A (n=89) with no previous local therapy and cohort B (n=83) with progression after local therapy or WBRT (3). The primary end point of overall intracranial objective response was 39% (29/74) in cohort A and 31% (20/65) in cohort B. The response rates were lower for V600K subgroup at 7% (1/15) and 22% (4/18) for cohorts A and B respectively, however numbers were very small. The median survival was 33 and 31 weeks for cohorts A and B respectively. In this study, dabrafenib was active despite progression after previous local therapy and was well tolerated, with adverse events consistent with previous studies. The numbers of spontaneous intracranial haemorrhages were lower with dabrafenib therapy (3).

Similarly there are studies and case reports of vemurafenib including a neoadjuvant approach enabling subsequent local therapies for lesions which were initially thought unresectable (40). A small prospective study of vemurafenib at 960 mg twice daily in 24 patients with BRAF V600 mutation positive with very poor prognosis and symptomatic unresectable melanoma brain metastasis (failing at least one previous therapy and requiring corticosteroids for symptom control) demonstrated activity (22). The median treatment

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duration was 3.8 (0.1-11.3) months, median PFS was 3.9 (95% CI, 3.0-5.5) months, median survival was 5.3 (95% CI, 3.9-6.6) months and overall partial response at both intracranial and extracranial sites was achieved in 10/24 (42%; 95% CI, 22.1-63.4) patients and stable disease in 9/24 (38%; 95% CI, 18.8-59.4) patients (22). A recent large phase 2 study of vemurafenib in 146 metastatic melanoma patients with active brain metastasis showed a similar objective response of 20% and a median PFS of 3.7 months (41). Retrospective case series have demonstrated activity of vemurafenib, supporting the results of the prospective studies (42).

Concordance of the BRAF mutation between metastases within an individual patient can vary by test used. In studies using immunohistochemistry, there was very high concordance between primary melanoma and multiple metastases, whereas studies using molecular tests varied (43,44). Despite this finding, the intracranial responses parallel extracranial responses (2,3,22). However acquired resistance to single agent BRAF inhibitors alone develops within 6-7 months of therapy (45) and is mainly driven by MAPK reactivation, via BRAF copy number gains, aberrant BRAF splicing, mutations in NRAS or MEK1/2 and upregulation of receptor tyrosine kinases (46-48). As predicted by preclinical studies, combination of a BRAF inhibitor and a MEK inhibitor, in comparison with BRAF inhibitor monotherapy, significantly improved response rates, median progression free/OS and decreased skin oncogenic toxicities, in phase 1/2 (n=162, median PFS 9.4 versus 5.8 months, RR 76% versus 54%) (45) and in phase 3 studies [COMBI-D (dabrafenib/trametinib versus dabrafenib): median PFS 9.3 versus 8.8 months (49), COBRIM (vemurafenib/cobimetinib versus vemurafenib): median PFS 9.9 versus 6.2 months] (50). These studies have not included patients with active brain metastasis and this is currently explored in several active phase 2 trials of single agent BRAF inhibitor (NCT01378975: vemurafenib), combination of BRAF/MEK inhibitor therapy (NCT02039947: COMBI-MB; NCT02230306: co-BRIM3) and of combination therapy in the neoadjuvant setting (NCT01978236) prior to resection of brain metastasis (*Table 1*) (51-53). Triplet combinations of BRAF/MEK inhibitors and pembrolizumab (NCT02130466) or other targeted drugs e.g., CDK 4/6 inhibitors (NCT02159066), are currently being explored in advanced melanoma without active brain metastases (51).

Several phase 2 studies of patients with V600 BRAF mutant metastatic melanoma, single agent trametinib or binimetinib demonstrated response rates of 17% to 25% in BRAF inhibitor naïve cohort (54-56) and a median progression-free survival (PFS) of 4.8 months compared with investigators choice chemotherapy (55), but has not been explored in brain metastases, and given its lesser activity than single agent BRAF inhibitor, not continued to be studied as a single agent.

MEK inhibitors and combination drug therapies in NRAS mutant melanoma

Several MEK inhibitors are in development in solid tumours, but the two most extensively investigated in melanoma are binimetinib (MEK162) and trametinib. MEK inhibitors have shown single agent activity in V600 BRAF mutated melanoma and NRAS mutated melanoma in patients without active brain metastases. In patients with NRAS mutated melanoma, single agent MEK 162, resulted in 11% (3/28 patients) partial response rates, 68% (19/28 patients) disease control rate and a PFS of 3.7 months (56). Phase 1/2 trials of combination of MEK inhibitors with a MDM2 inhibitor (AMG 232) (NCT02110355) and with a CDK 4/6 inhibitor (NCT02065063), amongst other combinations, are actively recruiting patients with NRAS mutated tumours, however active brain metastasis are excluded from these trials.

KIT inhibitors in c-kit mutant melanoma

There is currently no evidence of activity of c-kit inhibitors in patients with melanoma brain metastasis (57). The extracranial response rate to imatinib is approximately 30% with a median progression free survival of 3-4 months (58-60). The current management of c-kit mutation positive melanoma patients involves enrolment in clinical trials using c-kit inhibitor or immunotherapies or combination therapies targeting multiple independent pathways such MAPK, PI3K and immune mediated pathways.

Immunotherapy

Interleukin-2 (IL-2)

Historically high dose IL-2 has had a limited role in advanced melanoma in patients with good performance status and organ function (61-63) and no established role

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Table 1 Summary of active targeted therapy trials in melanoma brain metastases

Trial	Study details	Drugs	Nature of brain metastasis (BM)	Key exclusion	Primary endpoint
(NCT02039947): COMBI-MB; Cohorts A to D for V600 E, D, K, R mutations respectively	Phase 2	Dabrafenib 150 mg twice daily/trametinib 2 mg once daily until disease progression, death or unacceptable toxicity	Active	Neurological symptoms except in cohort D, leptomeningeal disease, ocular/mucosal melanoma, stereotactic radiosurgery within the 14 days and WBRT within 28 days of study treatment	Intracranial response rate at 2 years
NCT02230306 (co-BRIM3)	Phase 2	Vemurafenib 960 mg twice daily D1-28/cobimetinib 60 mg daily D1-21/28 days	Active	Leptomeningeal disease, increasing corticosteroid within 7 days of randomisation or BM requiring local therapy	Overall response rates
NCT01978236	Phase 2b, neoadjuvant setting	Cohort A: dabrafenib 150 mg twice daily for 7-14 days prior to surgery Cohort B: dabrafenib 150 mg twice daily/ trametinib 2 mg daily for 7-14 days prior to surgery	–	Uncontrolled neurological symptoms with stable corticosteroid dose, prior local therapy and leptomeningeal disease	Measurement of drug concentration within brain parenchymal lesions, extracranial lesions and blood plasma between day 8 and 15 of surgery
NCT01378975	Phase 2	Vemurafenib	Treated and untreated BM	Patients with increasing corticosteroid dose within 7 days of randomisation, leptomeningeal disease	Overall response rate in previously untreated brain metastasis
NCT01721603	Phase 2	Dabrafenib + stereotactic radiation. Patients will receive dabrafenib 150 mg twice daily and assessed with a 28-day MRI and those with stable disease/ partial response will have gamma knife radiosurgery	–	–	Six months distant brain metastasis free survival
NCT01781026	Phase two, neoadjuvant setting	Vemurafenib 960 mg BID for 4-8 weeks prior to surgery	Untreated and not amenable to local therapies	Leptomeningeal disease	Vemurafenib activity in untreated brain metastasis

WBRT, whole brain radiotherapy; BM, brain metastasis; MRI, magnetic resonance imaging. Active brain metastasis: symptomatic, treated and progressed, untreated.

in treating brain metastasis. The need for hospitalisation and the propensity to cause serious deleterious side effects including multiorgan failure, fatal cerebral edema and severe neurotoxicity limits its use. A large retrospective study showed some evidence of activity in patients with previously treated brain metastasis with little benefit in the untreated cohort (64). However a recent retrospective review of eight patients with stable brain metastasis showed progressive disease in 7/8 patients, with several grade three events (65).

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Checkpoint inhibitors

Ipilimumab

The fully humanised monoclonal antibody against cytotoxic T lymphocyte antigen-4 (CTLA4), ipilimumab, shows activity in melanoma brain metastasis, particularly if asymptomatic (23) and improves OS (66,67). A phase 2, multicentre, open-label study administered four doses of 10 mg/kg q3 weekly, followed by maintenance therapy, to 72 metastatic melanoma patients with brain metastasis; cohort A (n=51), asymptomatic patients and cohort B (n=21), symptomatic patients requiring corticosteroids (23). The global disease control was 18% [modified World Health Organisation (mWHO)] and 26% (immune-related response criteria-irRC) for cohort A and 5% (mWHO) and 10% (irRC) for cohort B. The median OS was 7 months for cohort A and 3.7 months for cohort B. Twelve patients (24%) in cohort A and two patients (10%) in cohort B achieved disease control within the brain. Interestingly, 33% (17/51) in cohort A and 24% (5/21) in cohort B, had prior WBRT. The most common adverse events were fatigue, diarrhoea, nausea, headache, rash and pruritis (23). A phase 2 study of ipilimumab and fotemustine showed an overall immune disease control rate of rate of 50% and a median progression free survival of 4.3 months, with increased incidence of both haematological and non-haematological toxicity (68). A phase 3 trial of this combination (EudraCT Number: 2012-004301-27, NIBIT-M2) is currently active (53).

PD1/PDL1 inhibitors and combinations

Long term exposure of T-cells to melanoma antigens leads to expression of programmed cell death 1 (PD-1) receptor (binds to its primary ligand PDL1 within the tumour microenvironment) and second ligand PDL2 by antigen presenting cells, resulting in negative regulation of the effector phase of T-cell responses against melanoma cells (69-71). A small study showed marked heterogeneity of PDL1 expression, by immunohistochemistry, between the primary and the metastasis and a positive correlation between PDL1 expression in locoregional metastasis and melanoma specific survival (72). PDL1 was expressed in about 47% of brain metastasis (72). Anti-PD1 antibody nivolumab and pembrolizumab have demonstrated highly durable response rates (RR 41% and 38% respectively), with minimal toxicity, in large phase 1 trials (73,74) and these were further confirmed in subsequent phase 3 trials of these agents versus chemotherapy in the first line (75) and in the second line setting after failure of anti-CTLA4 therapy (76). These agents in combination with ipilimumab are currently explored in several ongoing phase 2 trials in advanced melanoma patients with (NCT02374242, NCT02320058) and without (NCT01866319, NCT01721772) brain metastasis (51). A recent phase 1 trial of anti-PDL1 antibody (MPDL3280A) has shown activity in metastatic melanoma (77).

Anti-PD1 Brain Collaboration (ABC) (NCT02374242) is an Australian Brain randomised phase 2 trial exploring the activity of anti-PD1 antibody alone and in combination with ipilimumab, in melanoma brain metastasis (51). Eligible patients are those with histologically confirmed metastatic melanoma, measurable brain lesions (5-40 mm) and immunotherapy naïve. Refractoriness to prior BRAF therapy does not preclude participation in the trial. Six patients will initially be enrolled into cohort 1 (asymptomatic and previously untreated brain metastases) and cohort 2 (patients with previously treated brain metastases that have progressed after local treatment, and/or patients who have neurological symptoms related to brain metastases, and/or have leptomeningeal disease). Patients in cohort 1 and 2 will receive nivolumab 3 mg/kg, every 2 weeks. An interim safety analysis will be conducted when six patients from cohort 1 have received 6 weeks of therapy with nivolumab; to assess adverse events related to brain metastases, such as intracranial haemorrhage, seizure or other neurological toxicity. If these adverse events are acceptable (occur in ≤2 of the six patients at a CTCAE grade no higher than 2), then the study will be extended to include an additional cohort of 30 patients with asymptomatic and previously untreated brain metastases to a combination of nivolumab (1 mg/kg, every 2 weeks, for four doses, then continue 3 mg/kg every 2 weeks subsequently) and ipilimumab (3 mg/kg, every 3 weeks for four doses). The primary endpoint is the intracranial response rate (complete and partial response in intracranial metastases as measured using RECIST 1.1 criteria (modified for brain metastasis). Another phase 2 trial (NCT02320058) is also exploring the activity of combination of ipilimumab and nivolumab in active melanoma brain metastases (51).

Chemotherapy

Fotemustine and temozolomide have been trialled in melanoma brain metastasis but have shown disappointing

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results, limiting its role in clinical management in this setting. A phase 2 study of temozolomide (150 mg/m^2/d ×5 days every 28 days) in 151 patients with previously untreated brain metastasis showed a response rate of 6% and a median OS of 3.2 months (17). A phase 3 trial of fotemustine versus dacarbazine, in 43 patients with melanoma brain metastasis, showed a brain response rate of only 5.3% for fotemustine and 0% for dacarbazine (78).

Local therapies for melanoma brain metastasis

The evidence for use of local therapies in treating melanoma brain metastasis is based on large retrospective melanoma specific studies or based on inference from non-melanoma studies (79,80). Surgery is useful in managing solitary or limited intracranial disease especially those with symptoms or complications such as mass effect or haemorrhage and there is some evidence of improved survival (79,81,82). Radiosurgery may be used for small asymptomatic non-haemorrhagic lesions (83,84), and reported 12 months local control rates ranges from 52% to 75% (83,85,86). The addition of SRS to WBRT (87,88) or surgery (89,90) improves local control and distant brain free survival, but does not affect OS. A phase 3 trial of WBRT following local treatment of melanoma brain metastasis is currently underway, testing distant intracranial failure, OS, neurocognitive function and quality of life (NCT01503827). The WBRT is generally reserved for diffuse or leptomeningeal disease and the combination of WBRT and targeted therapy vandetanib (EudraCT Number: 2011-0006661-12, sponsor protocol number: OCTO_022) and ipilimumab (EudraCT Number: 2013-001132-22, sponsor protocol number: GEM-1202) are currently being tested in phase 2 trials (53). The addition of WBRT to SRS may affect the quality of life through neurocognitive decline (91,92) and needs careful consideration while managing such patients.

Approach to management of metastatic melanoma with brain metastasis

The advent of new targeted therapies, immune modulating therapies and sandwiching local therapies with systemic therapies has changed the way melanoma brain metastasis are managed, and the prognosis for such patients. The treatment decisions, based on key factors such as mutation status, performance status, burden and pace of extracranial disease and active brain metastasis, should be made in consultation with a multidisciplinary team of neurosurgeons, medical oncologist, radiation oncologist and others involved in the patient's care.

Participation in a clinical trial should be encouraged, if an appropriate trial is available. For BRAF mutated patients, depending on the key factors listed above, the systemic therapy of choice may be either a targeted BRAF inhibitor therapy, preferably in combination with a MEK inhibitor, or an immune check point inhibitor. Until there is data from the anti-PD1 brain trials, check point inhibitors should be given with or shortly after local brain therapy as the response rate in brain is not high. For BRAF wild-type patients, immune check point inhibitor therapy is the systemic therapy of choice, usually given concurrently with or shortly after local brain therapy. Although ipilimumab is recommended first line outside of a clinical trial, and anti-PD1 therapy is commenced only after progression on ipilimumab, this paradigm may change, and anti-PD1 therapy may become the first-line choice alone or in combination with ipilimumab. The slow onset of response and low response rate with ipilimumab needs careful monitoring and in instances of concerns of early disease progression, changing early to anti-PD1 therapy should be considered. A schematic representation of management of metastatic melanoma is outlined in *Figure 2* (25).

Key points

- Melanoma brain metastasis remains a major clinical problem and a multidisciplinary approach to management should be adopted.
- Enrolment into an appropriate clinical trial, when available, should be encouraged as the first step towards managing melanoma brain metastases.
- Not all patients with melanoma brain metastases require systemic therapy, e.g., solitary brain metastasis with absence of extracranial disease.
- BRAF inhibitors have shown a high rate of intracranial objective responses that parallel extracranial responses and should be considered in BRAF mutated melanoma especially in symptomatic patients with a high disease burden (*Table 2*).
- The focus for immune therapies has shifted to incorporate anti-PD1 antibodies. The FDA in the USA

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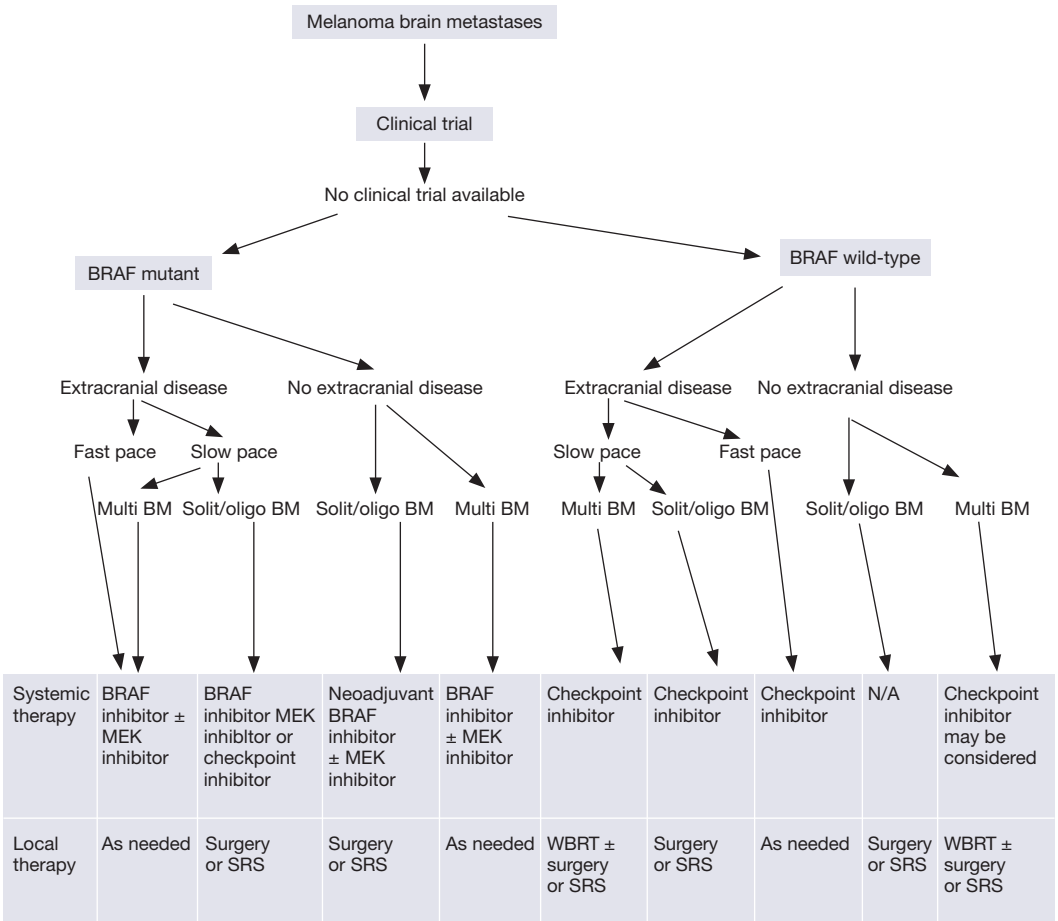

Figure 2 Algorithm for managing melanoma brain metastases. Solit/oligo BM, solitary or oligometastatic brain metastasis; multi BM, multiple brain metastasis; SRS, stereotactic radiotherapy; WBRT, whole brain radiotherapy.

approved anti-PD1 therapy after ipilimumab progression, however results of phase 3 trials using first-line anti-PD1 antibodies or in combination with ipilimumab, will likely place anti-PD1 therapy as a backbone therapy, particularly for BRAF wild type melanoma with a high disease burden.

- In asymptomatic brain metastasis, not requiring steroid therapy, ipilimumab offers objective responses and survival benefit, similar to that seen with extracranial disease.
- Clinical trials of therapies specifically targeting NRAS or c-kit mutations in melanoma, have excluded patients with active brain metastases to date, largely because of the need to first determine combinations of therapies with good activity in extracranial metastases. As we determine optimal combinations to take forward into trials of patients with active brain metastases, these patients should be encouraged to participate in trials of immunotherapies, and trials for BRAF wildtype melanoma.

Conclusions

Brain metastasis is frequently encountered in clinical practice and while research has opened up several pathways of treatment, the prognosis remains guarded. Although our experience with targeted and immune therapies shows promising activity in melanoma brain metastases, clinical trial evidence of activity for many of these drugs, especially in combination, is currently in progress. Enrolment into clinical trials is essential, to develop evidenced-based practice paradigms for management of this difficult disease,

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Table 2 Summary large prospective clinical trials in melanoma brain metastases

Trial	Phase	Patients with BM (n)	Active BM	Treatment	Brain ORR [%]	Extracranial ORR [%]	Median PFS (months)	Median OS (months)
Long *et al.* (3)	2	Cohort A* =89; Cohort B** =83	Yes	Dabrafenib	Cohort A: V600E 39.2; V600K 6.7 Cohort B: V600E 30.8; V600K 22.2	37.8; 0 30.8; 27.8	4.02; 2.02 4.15; 3.97	8.27; 4.07 7.85; 5.47
Kefford *et al.* (41)	2	Cohort 1*** =90; Cohort 2**** =56	Yes	Vemurafenib	18 20	– –	4 4.3	7 6.95
Falchook *et al.* (2)	1	10	Yes	Dabrafenib	90	69	4.2	–
Dummer *et al.* (22)	Pilot	24	Yes	Vemurafenib	16	62	3.9	5.3
Margolin *et al.* (23)	2	Cohort A =51 (asymptomatic); Cohort B =21 (symptomatic)	Yes	Ipilimumab	16; 5	10; 5	1.4; 1.2	7; 3.7
Di Giacomo *et al.* (68)	2	20	Subgroup	Ipilimumab + fotemustine	DCR 50	DCR 46.5	4.5	13.4
Agarwala *et al.* (17)	2	151	Yes	Temozolomide	6	13.5%[#]	1.1	3.2
Avril *et al.* (78)	3	43	Subgroup	Fotemustine (n=22) DTIC (n=21)	5.9; 0	13.4; 6	–	–

Cohort A*, untreated asymptomatic brain metastases; Cohort B**, previous brain directed local therapy but progressed according to RECIST 1.1; Cohort 1***, previously untreated BM; Cohort 2****, previously treated BM; [#], reported from study titled 'Randomised phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma' (93).

to study mechanisms of intracranial response and resistance to treatment, and to devise better ways of treatment.

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