Evolving treatment options for melanoma brain metastases

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Melanoma is a leading cause of lost productivity due to premature cancer mortality. Melanoma frequently spreads to the brain and is associated with rapid deterioration in quality and quantity of life. Until now, treatment options have been restricted to surgery and radiotherapy, although neither modality has been well studied in clinical trials. However, the new immune checkpoint inhibitors and molecularly targeted agents that have been introduced for treatment of metastatic melanoma are active against brain metastases and offer new opportunities to improve disease outcomes. New challenges arise, including how to integrate or sequence multiple treatment modalities, and current practice varies widely. In this Review, we summarise evidence for the treatment of melanoma brain metastases, and discuss the rationale and evidence for combination modalities, highlighting areas for future research.

Introduction

Melanoma is the third most common cause of brain metastasis after lung and breast cancers. The biological predisposition for melanoma to spread to the brain is not fully understood, but the brain is frequently a site of metastasis at the end stages of the disease. Although around 7% of patients with melanoma present with brain involvement at diagnosis, up to 60% of all patients with melanoma will develop brain metastases during the course of their illness, including 25% with a solitary brain lesion. Surgery, radiotherapy, and radiosurgery have traditionally been used in the management of melanoma brain metastases either as single-modality treatments or in combination. The median overall survival of patients with untreated brain metastases is less than 3 months, but might be longer if aggressive loco-regional treatment is possible. Immunomodulators and targeted agents against mutations in the BRAF gene have become established treatment for patients with metastatic melanoma, offering a survival benefit. Here, we review the present understanding and evolving multimodal management of melanoma brain metastases, and the challenges of how best to integrate new systemic therapies.

Risk factors for melanoma brain metastases

A review of 702 patients with melanoma brain metastases identified male sex, head and neck or truncal primary, mucosal melanoma, nodular or acral lentiginous histologies, and visceral or nodal metastases as risk factors for melanoma brain metastases, although the evidence is not entirely consistent. For example, a study of similar size (686 patients) did not find that truncal primaries increase the risk of brain metastases; however, in agreement with other studies, the investigators noted an increased risk of brain metastases for head and neck primaries, and a substantially reduced risk for limb primaries. A high M stage, increased serum lactate dehydrogenase (LDH) concentrations, three or more visceral metastases, and a high Clark’s level and Breslow’s thickness of the primary tumour have also been reported to increase the risk of melanoma brain metastases.

Data correlating melanoma mutations with the development of melanoma brain metastases are conflicting. In a series of 677 patients, brain metastases were reported in 24% of patients with BRAF-mutant melanoma and 23% of patients with NRAS-mutant melanoma, compared with 12% of patients with wild-type tumours. Among 105 patients with melanoma brain metastases in this study, 61 (58%) patients had BRAF-mutant melanoma and 24 (23%) had NRAS-mutant disease, whereas 20 (19%) patients were wild-type for both genes (p=0.0076). However, no correlation was reported in another study.

Imaging and response assessment

The radiological appearance of melanoma brain metastases varies substantially. CT scanning generally shows extensive oedema with a slightly hyperdense irregular lesion (or lesions), which enhances heterogeneously after contrast administration. Melanomas are generally highly vascular and intracerebral haemorrhage is common, which might be evident on CT imaging. The typical so-called melanotic pattern of brain metastasis is hyperintense on T1-weighted images and hypointense on T2-weighted images, whereas the so-called amelanotic pattern of brain metastasis is hypointense or isointense on T1-weighted images and hyperintense or isointense on T2-weighted images. Subtle subependymal and leptomeningeal lesions are also characteristic of melanoma. Such varied appearances of melanoma brain metastases create difficulties in diagnosis, treatment, and response assessment. Furthermore, both systemic therapy and radiotherapy can generate changes in contrast enhancement, pressure effect, and intratumoural haemorrhage. After radiosurgery, T2-weighted imaging typically shows changes in perilesional oedema with central hypointensity after 2–6 months, followed by blurring of enhancing tumour and reduction in the volume of enhancing tumour on T1-weighted gadolinium-enhanced images.

Since there is substantial variation in the response assessment criteria used in previous neuro-oncology trials, new recommendations were proposed by the Response Assessment in Neuro-Oncology Brain Metastases working group in June, 2015. According to the new criteria, a radiological progression of target or non-target lesions after immunotherapy and radiosurgery should be regarded as pseudoprogression rather than progression (figure I). If progression is suspected during
immunotherapy, continued treatment and short interval scans are advised. After radiosurgery, if radionecrosis is suspected, advanced imaging techniques, such as perfusion MRI and magnetic resonance spectroscopy, might be needed.

**Treatment of melanoma brain metastases: limitations of the evidence base**

The quality of the efficacy data for surgery, radiosurgery, radiotherapy, and systemic treatment in the management of melanoma brain metastases is variable. Most interventional studies assessing surgery or radiotherapy, or a combination of both, to treat brain metastases have recruited patients with disease originating from various primary sites, with very few studies confined to patients with melanoma. Therefore, interpretation of the available data to inform clinical practice is difficult. In advanced disease, the poor prognosis associated with melanoma brain metastases and inadequate penetration of cytotoxic drugs across the blood–brain barrier meant that, in the past, these patients were mostly excluded from clinical trials of systemic therapies for metastatic melanoma. The situation is changing, with more studies offering entry for patients with melanoma brain metastases if their disease is stable. The advent of active systemic therapies means that melanoma surveillance is increasingly likely to include proactive imaging of both the body and the brain. Although it is reasonable to assume that this change in practice will identify more metastases sooner in asymptomatic patients than does present practice, whether this intervention affects the overall outcome is unknown.

**Single-modality local treatment**

**Surgery**

In patients with a solitary brain metastasis, surgery can result in rapid improvement in neurological symptoms. The best supportive evidence for surgery as the standard of care is retrospective. In the study of 686 patients with melanoma brain metastases, median overall survival for patients selected for surgery (8·7 months) or surgery plus radiotherapy (8·9 months) was significantly longer than that for patients given radiotherapy alone (3·4 months) or supportive care (2·1 months; p<0.001).

**Whole-brain radiotherapy**

Melanoma has been regarded as a radioresistant tumour, although a wide variation in radiosensitivity has been reported both in vitro and clinically. The median overall survival with whole-brain radiotherapy (WBRT) is 2–5 months, with 1-year survival of less than 13%. Patients younger than 65 years with a good performance status (Karnofsky performance score [KPS] ≥70) and no extracranial disease have the best survival after WBRT. Studies by the Radiation Therapy Oncology Group suggested that the standard fractionation for WBRT is 30 Gy in ten fractions over 2 weeks, and a meta-analysis showed that none of the other fractionations studied was superior in terms of overall survival, neurological function, or symptom control.

The role of WBRT in the treatment of melanoma brain metastases needs to be reassessed in view of the wide availability of new systemic therapies. Of note, WBRT can negatively affect quality of life and neurocognitive functions. A randomised study of neurocognitive function using the Hopkins Verbal Learning Test—Revised total recall showed a significant decline in learning and memory function at 4 months after WBRT plus stereotactic radiosurgery (SRS) compared with SRS alone (mean posterior probability of decline 52% vs 24%), leading to discontinuation of the study after enrolment of only 58 patients. Damage to neural progenitor cells in the subgranular zone of the hippocampus is thought to cause radiation-induced neurocognitive decline. A phase 2 study showed that conformal avoidance of the hippocampus during WBRT for brain metastases results in the preservation of memory and a better quality of life compared with historical controls. Examination of the MRI scans of a cohort of 77 patients with melanoma in the ANZMTG trial did not show any metastases within the hippocampus, and only four (5%) patients had metastases within 5 mm of the hippocampus, suggesting that hippocampal-sparing WBRT might not compromise efficacy. A randomised controlled trial of patients with melanoma brain metastases is comparing WBRT (30 Gy in ten fractions) with whole-brain helical tomotherapy and hippocampal-sparing WBRT (30 Gy in ten fractions) with an integrated boost of 50 Gy to the brain metastases (table 1; appendix).

**Stereotactic radiosurgery**

SRS allows individual metastases to be treated with a high radiation dose while sparing surrounding normal brain tissues using Gamma Knife or linear accelerator.
techniques. In selected patients with one to four metastases measuring less than 3–4 cm, SRS yields a good local control (more than 85%) and median survival of 5–11 months (table 2; appendix). Since no comparative studies of surgery versus SRS have been done, whether SRS is superior or equivalent to surgery is unclear. Additionally, the population of patients who undergo SRS might vary according to patient and tumour characteristics and the expertise of local treatment centres. Generally, surgery is favoured for solitary metastases in accessible locations and when an immediate relief of neurological symptoms is warranted. SRS might be the preferred option for up to three metastases that are 3 cm or smaller in diameter, especially those in inaccessible or eloquent locations. Although sufficient evidence from published work supports the option of SRS for fewer than four metastases, studies have reported the use of SRS for patients with ten or more lesions.29 The UK national guideline uses total tumour volume rather than the number of metastases for consideration for SRS. The accepted upper limit for SRS is 20 cm³ tumour volume, which is equivalent to a single tumour of 3·2 cm in diameter.

### Combined-modality local treatment

**WBRT versus surgery plus WBRT**

Three randomised trials have compared WBRT with the combination of surgery followed by WBRT in patients diagnosed with a single brain metastasis. However, in all of these studies, the number of patients with melanoma brain metastases was small, and the reported outcomes were for the whole cohort of patients. In a study of 48 patients (three with melanoma brain metastases),27 the combined-modality treatment was associated with a longer median overall survival (40 weeks vs 15 weeks; p=0·01), a lower risk of local recurrence (20% vs 52%; p=0·02), and a longer median functional independence (38 weeks vs 8 weeks; p<0·005) than was WBRT alone. In a study of 63 patients with single brain metastases (six with melanoma brain metastases),28 surgical excision followed by WBRT (40 Gy in 20 fractions) resulted in improved median overall survival (10 months vs 6 months; p=0·04) compared with that in WBRT alone. Patients with extracranial disease had the greatest survival advantage with combined-modality treatment compared with WBRT alone (median overall survival 12 months vs

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Table 1: Clinical trials in progress

<table>
<thead>
<tr>
<th>Type of trial</th>
<th>Intervention</th>
<th>Main eligibility</th>
<th>Primary outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANZMTG 01.07 (WBRT Mel)26</td>
<td>Phase 3 (N=200) WBRT vs monitoring following local treatment of brain metastases</td>
<td>1–3 brain metastases treated with surgery or SRS and ECOG-PS 0–2</td>
<td>Distant intracranial failure</td>
</tr>
<tr>
<td>NCT01644591</td>
<td>Phase 3 (N=80) SRS vs WBRT (30 Gy in 10 fractions)</td>
<td>&gt;3 and ≤10 brain metastases and KPS ≥70</td>
<td>Time to local failure and neurocognitive decline at 4 months using HVLT-R score</td>
</tr>
<tr>
<td>DRKS0000512727</td>
<td>Randomised controlled (N=50) WBRT (30 Gy in 10 fractions) compared with whole-brain helical tomotherapy and hippocampal-sparing WBRT (30 Gy in 10 fractions) with an integrated boost (50 Gy) to metastases</td>
<td>&gt;1 brain metastasis and KPS ≤60</td>
<td>Toxicity and side-effects</td>
</tr>
<tr>
<td>NCT01721603</td>
<td>Phase 2 (N=40) SRS plus dabrafenib</td>
<td>1–4 brain metastases and none &gt;3 cm</td>
<td>Improvement in 6-month distant brain metastasis-free interval</td>
</tr>
<tr>
<td>NCT0215139 (GEM)</td>
<td>Phase 2 (N=66) WBRT (30 Gy in 10 fractions) plus ipilimumab</td>
<td>Radiological brain metastases</td>
<td>1-year survival</td>
</tr>
<tr>
<td>NCT01703507</td>
<td>Phase 1 (N=24) WBRT plus ipilimumab (for ≤5 metastases) or SRS plus ipilimumab (1–4 metastases of ≤4 cm)</td>
<td>Brain metastases with ECOG-PS 0–1</td>
<td>Maximum tolerated dose of ipilimumab</td>
</tr>
<tr>
<td>NCT02097732</td>
<td>Randomised phase 2 (N=40) Two doses of ipilimumab before SRS plus two doses after SRS vs SRS followed by four doses of ipilimumab</td>
<td>1–4 brain metastases (at least one lesion ≤5 mm) and ECOG 0–1</td>
<td>6-month local control</td>
</tr>
<tr>
<td>NCT02039947</td>
<td>Phase 2 (N=120) Dabrafenib plus trametinib</td>
<td>At least one measurable brain metastasis in BRAF mutation-positive melanoma</td>
<td>Intracranial response</td>
</tr>
<tr>
<td>NCT02230306 (co-BRIM-B)</td>
<td>Phase 2 (N=72) Vemurafenib plus cobimetinib</td>
<td>BRAF mutation-positive melanoma with at least one measurable lesion of 0·5–4 cm</td>
<td>Overall response</td>
</tr>
<tr>
<td>NCT0220058</td>
<td>Phase 2 (N=48) Nivolumab plus ipilimumab, followed by nivolumab monotherapy</td>
<td>At least one measurable brain lesion and ECOG 0–1</td>
<td>CNS clinical benefit at 6 months</td>
</tr>
<tr>
<td>NCT02085070</td>
<td>Phase 2 (N=40) Pembrolizumab</td>
<td>Asymptomatic, steroid-free brain metastases from melanoma and non-small-cell lung cancer</td>
<td>Response</td>
</tr>
<tr>
<td>NCT02460068 (NIBIT-M2)</td>
<td>Phase 3 (N=168) Fotemustine vs fotemustine plus ipilimumab</td>
<td>New asymptomatic brain metastases after WBRT or SRS, and ECOG 0–2</td>
<td>Overall survival</td>
</tr>
<tr>
<td>ACTRN12614001315606 (ABC)</td>
<td>Phase 2 (N=75) Nivolumab vs nivolumab plus ipilimumab</td>
<td>At least one measurable lesion of 0·5–4 cm and ECOG 0–2</td>
<td>Intracranial response</td>
</tr>
</tbody>
</table>

Series of radiosurgery for melanoma brain metastases

Only series with 50 or more patients are included. See appendix for full list of references. NR=not reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients (number of metastases)</th>
<th>Radiosurgery dose (Gy)</th>
<th>% Local control (at median follow-up)</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al</td>
<td>103 (153)</td>
<td>18</td>
<td>73% (8 months)</td>
<td>7.5</td>
</tr>
<tr>
<td>Liew et al</td>
<td>333 (1570)</td>
<td>18</td>
<td>73% (4 months)</td>
<td>8.3</td>
</tr>
<tr>
<td>Gaudy-Marquette et al</td>
<td>106 (221)</td>
<td>25</td>
<td>84% (NR)</td>
<td>5.1</td>
</tr>
<tr>
<td>Seung et al</td>
<td>55* (140)</td>
<td>19</td>
<td>77% (12 months)</td>
<td>8.7</td>
</tr>
<tr>
<td>Yu et al</td>
<td>122 (332)*</td>
<td>20</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td>Herfarth et al</td>
<td>64 (122)</td>
<td>20</td>
<td>81% (12 months)</td>
<td>10.6</td>
</tr>
<tr>
<td>Radbill et al</td>
<td>51 (188)*</td>
<td>17.3</td>
<td>81% (6-25 months)</td>
<td>6.5 (19.0 months if single lesion; 14.0 months if SRS)</td>
</tr>
<tr>
<td>Mathieu et al</td>
<td>244 (754)</td>
<td>18</td>
<td>86% (5-3 months)</td>
<td>5.3 (13.0 months if controlled systemic disease)</td>
</tr>
<tr>
<td>Bemard et al</td>
<td>54 (103)*</td>
<td>24</td>
<td>68% (12 months)</td>
<td>NR (1-year OS 25%)</td>
</tr>
<tr>
<td>Marcus et al</td>
<td>125 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>6.9</td>
</tr>
<tr>
<td>Neal et al</td>
<td>129* (185)</td>
<td>18.8</td>
<td>81% at 12 months; 53% at 24 months</td>
<td>6.7 (1-year OS 26%)</td>
</tr>
</tbody>
</table>

Only series with 50 or more patients are included. See appendix for full list of references. NR=not reported.

RPA1=recursive partitioning analysis class 1. OS=overall survival. *Some patients also had surgery, whole-brain radiotherapy, stereotactic radiosurgery, or a combination of local treatments.

Table 2: Series of radiosurgery for melanoma brain metastases

7 months; p=0.02). However, another randomised trial did not replicate these benefits from surgery.

Surgery versus surgery plus WBRT or SRS

The benefits of WBRT after complete resection of a single brain metastasis are also unclear. In a randomised study of 95 patients (two with melanoma brain metastases), addition of WBRT after complete resection of a single metastasis (n=49) resulted in less frequent recurrence of a tumour in the brain (18% vs 70%; p=0.001) than did no WBRT after surgery (n=46). Although patients who received WBRT were less likely to die from neurological causes than were patients without WBRT, no overall survival advantage was reported.

A non-randomised series on SRS boost to the metastatectomy cavity shows acceptable local control, but with a risk of radionecrosis and a need for long-term steroids. Among 59 patients studied, the nine patients with melanoma had a median overall survival of 15-25 months and the proportion of patients with local control was 98-3%. The frequency of SRS complication was 2-4%. Salvage WBRT was needed in 25 (42%) patients.

WBRT versus SRS or surgery plus WBRT

The role of WBRT after definitive local treatment for one to three brain metastases has been investigated in the EORTC 22952-26001 study, in which 359 patients (18 with melanoma brain metastases) undergoing surgery (n=160) or SRS (n=199) were randomised to no further treatment or WBRT (30 Gy in ten fractions). Although WBRT improved 2-year relapse (27% for WBRT plus surgery vs 59% for surgery alone [p<0.001]; 31% for WBRT plus SRS vs 19% for SRS alone [p=0.04]) and prevented more new sites of relapse than no further treatment, no improvement in overall survival was reported.

Two randomised studies compared the benefit of combined SRS and WBRT with WBRT alone in patients with brain metastases. In the RT0G 9508 study of 333 patients with one to three metastases (14 with melanoma brain metastases), 167 patients received combined-modality treatment and 164 received WBRT alone (two patients were excluded: one had no confirmation of eligibility and the other had too many metastases). Even though disease stabilisation or an improvement in KPS was reported in 43% of patients who received combined-modality treatment, compared with 27% of patients who received WBRT alone (p=0.03), the median overall survival did not differ (6.5 months vs 5.7 months; p=0.14).

In another randomised study of 27 patients with two to four brain metastases (including five with melanoma brain metastases) comparing WBRT alone (n=14) with WBRT plus radiosurgery (n=13), 1-year local failure was 100% in patients who received WBRT, compared with only 8% in patients who had the combined-modality treatment (p=0.0016). Patients who received WBRT alone had a non-significant inferior median overall survival compared with those who received WBRT plus radiosurgery (7.5 months vs 11.0 months; p=0.22).

A retrospective series of WBRT (median dose 37.5 Gy) followed by SRS (median dose 17 Gy) in 122 patients (16 with melanoma brain metastases) with a single brain metastasis reported a median overall survival of 56 weeks and local control in 86% of patients with combined-modality treatment (table 3; appendix).

Melanoma-specific graded prognostic assessment

Sperduto and colleagues studied 481 patients with newly diagnosed melanoma brain metastases, who were given WBRT (n=86), surgery plus WBRT (n=29), surgery plus WBRT and SRS (n=25), SRS alone (n=221), WBRT plus SRS (n=89), or surgery plus SRS (n=30). The investigators identified KPS and the number of brain metastases as significant prognostic factors for overall survival and derived scoring criteria for a melanoma-specific graded prognostic assessment. Using these criteria, patients with a KPS of less than 70 and more than three metastases had a median overall survival of 3-4 months, whereas patients with a KPS of 90-100 and one metastasis had a median overall survival of 13-2 months.

On multivariate analysis, the median survival of patients with melanoma brain metastases was also affected by treatment modality. The risk of death was significantly lower with combined-modality treatment compared with a median overall survival of 2.9 months in patients who had WBRT alone, median survival was...
Many studies have assessed the role of cytotoxic chemotherapy in melanoma brain metastases, but none have reported significant activity. Dacarbazine has historically been the standard cytotoxic chemotherapy for this disease, but it does not cross the blood–brain barrier. Temozolomide, a derivative of dacarbazine, can penetrate the CNS, but randomised trials did not show superiority over dacarbazine for either systemic or brain metastases. Addition of temozolomide to radiotherapy or SRS has no survival advantage (table 4; appendix). In a single-arm phase 2 trial of fotemustine treatment, 24% of patients with melanoma brain metastases had an overall response. However, a subsequent phase 3 trial comparing fotemustine with dacarbazine identified a lower proportion of patients with an overall response after fotemustine treatment (15%). The addition of WBRT to fotemustine did not result in a significant benefit in response or overall survival compared with fotemustine alone.

**Immunomodulators**

Melanoma is one of the most immunogenic tumours, evidenced by occasional spontaneous regression, the presence of tumour-infiltrating lymphocytes, and clinical responses to immune stimulation. The cytokines interleukin 2 and interferon have been extensively studied as treatments for early and advanced melanoma. Interleukin 2 is a cytokine produced by activated T cells that increases proliferation and activation of cytotoxic T cells, natural killer cells, and monocytes. The antitumour activity of recombinant interleukin 2 was shown mainly in phase 2 clinical trials in which the proportion of patients with a response reached 16% in patients with advanced melanoma, but its approval for use in patients with
advanced melanoma was based on the durability of the responses and the absence of alternative options. Interleukin 2 toxicity depends on the dose, route, and duration of administration, with high doses seeming to be the most active but also most toxic. High-dose interleukin 2 has proved disappointing for treatment of brain metastases: in a retrospective review of patients with previously untreated brain metastases (n=36), only two (6%) patients had a response, although this was higher for patients who had received previous treatment (five [18%] of 27; p=0.031).

CTLA-4 is a key negative regulator of T-cell activity, and the anti-CTLA-4 monoclonal antibody, ipilimumab, was developed to potentiate antitumour T-cell activity. Two international phase 3 trials comparing ipilimumab with standard of care in previously treated brain metastases (MDX010-20) and untreated (CA184-024) patients with metastatic melanoma showed, for the first time, significant improvement in overall survival with ipilimumab; on this basis, ipilimumab became the new standard of care. MDX010-20 allowed entry of patients with stable, treated brain metastases, whereas CA184-024 excluded all patients with brain metastases. MDX010-20 was a three-group trial (n=676) comparing ipilimumab (3 mg/kg) plus gp100, ipilimumab alone, and gp100 alone, and it included 77 (11%) patients with a history of brain metastases who did not need steroids. Similar benefits were seen in patients with brain metastases and those without, with HRs for survival of 0.70 versus 0.69 (in the ipilimumab plus gp100 group) and 0.76 versus 0.64 (in the ipilimumab alone group). Ipilimumab does not itself cross the blood–brain barrier, but studies have shown that activated T cells can migrate to the brain and generate an antitumour response.

A subsequent single-arm phase 2 study (CA184-042) assessed the role of ipilimumab in 72 patients with melanoma brain metastases. At baseline, 51 patients were asymptomatic and steroid free, 17 (33%) of whom had had previous WBRT, and 21 patients were symptomatic and on minimal doses of steroids, five (24%) of whom had had previous WBRT. The study reported an equivalent proportion of patients achieving an overall response (25%) for intracranial and extracranial disease sites. The median survival of patients with asymptomatic brain metastases was 7.0 months.

Figure 2: Proposed algorithm for management of melanoma brain metastases
KPS=Karnofsky performance score. SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy. *Key research opportunities for future clinical trials.
A single-arm phase 2 trial (NIBIT-M1)\(^48,49\) tested the combination of ipilimumab with fotemustine in metastatic melanoma, including 35 patients with brain metastases, achieving 42% PR or SD and 16% control rate. For patients with brain metastases, the median immune-related progression-free survival was 4.5 months, and the median brain-specific progression-free survival was 4.9 months. Updated results of this study\(^50\) reported a 3-year survival of 28.5%, compared with 19% (1-year survival) and 10% (2-year survival) for patients with symptomatic brain metastases.

The US expanded-access study investigating ipilimumab in metastatic melanoma, CA184-045,\(^5\) allowed entry of patients with stable, asymptomatic brain metastases. 165 patients enrolled with brain metastases, all received 10 mg/kg of ipilimumab, and 1-year survival was reported to be 20%. Taken together, these data support that ipilimumab should be regarded as an active treatment for patients with melanoma brain metastases.

A single-arm phase 2 trial (NIBIT-M1)\(^48,49\) tested the combination of ipilimumab with fotemustine in 86 patients with metastatic melanoma, including 20 patients with asymptomatic brain metastases. 40 (47%) patients, including ten with brain metastases, achieved good disease control. For patients with brain metastases, the median immune-related progression-free survival was 4.5 months, and the median brain-specific progression-free survival was 3.0 months. Updated results of this study\(^50\) reported a 3-year survival of 28.5% for the whole study population and 27.8% for the cohort with melanoma brain metastases (seven patients lived beyond 2 years). The contribution of fotemustine in combination with ipilimumab to outcome improvement beyond 2 years). The contribution of fotemustine in combination with ipilimumab to outcome improvement beyond 2 years).

### Table 4: Published studies of ipilimumab and BRAF-targeted agents with or without radiotherapy

<table>
<thead>
<tr>
<th>Study type</th>
<th>Study population</th>
<th>Intervention</th>
<th>Cranial response</th>
<th>Median overall survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margolin et al</td>
<td>Phase 2 (N=72) Cohort A: asymptomatic brain metastases; Cohort B: symptomatic brain metastases</td>
<td>Ipilimumab</td>
<td>(Global=CR, PR, or SD)</td>
<td>Cohort A: 7.0 (2-year survival 26%); Cohort B: 3.7 (2-year survival 10%)</td>
</tr>
<tr>
<td>Weber et al</td>
<td>Retrospective (N=12) Stable brain metastases in a phase 2 study</td>
<td>Ipilimumab</td>
<td>42% PR or SD</td>
<td>14</td>
</tr>
<tr>
<td>Konstantinou et al</td>
<td>Retrospective (N=38) Stable brain metastases</td>
<td>Ipilimumab</td>
<td>3 (8%) PR and 5 (13%) SD; 16% control rate</td>
<td>3.3</td>
</tr>
<tr>
<td>Di Giacomo et al</td>
<td>Phase 2 (subset of NIBIT-M1 trial; N=20) Asymptomatic brain metastases</td>
<td>Ipilimumab plus fotemustine</td>
<td>ir-RC 50%</td>
<td>12.7 (3-year OS 28%)</td>
</tr>
<tr>
<td>Knisely et al</td>
<td>Retrospective (N=77) Symptomatic brain metastases</td>
<td>SRS alone (n=42) vs SRS plus ipilimumab (n=35)</td>
<td>NR</td>
<td>4.9 vs 21.3 (2-year survival 19.7% vs 47.2%)</td>
</tr>
<tr>
<td>Mathew et al</td>
<td>Retrospective (N=58) Symptomatic brain metastases</td>
<td>SRS (n=23) vs SRS plus ipilimumab (n=25)</td>
<td>NR (6-month local control 63% vs 65%)</td>
<td>NR (6-month OS 46% vs 56%)</td>
</tr>
<tr>
<td>Silk et al</td>
<td>Retrospective (N=70) Symptomatic brain metastases</td>
<td>WBRT or SRS (n=17) vs WBRT or SRS plus ipilimumab (n=33)</td>
<td>9% vs 40%</td>
<td>5.3 vs 18.3</td>
</tr>
<tr>
<td>Gerber et al</td>
<td>Retrospective (N=13) Symptomatic brain metastases</td>
<td>Ipilimumab plus WBRT</td>
<td>ir-RC 56%</td>
<td>NR</td>
</tr>
<tr>
<td>Queirolo et al</td>
<td>Prospective expanded access programme (N=146)</td>
<td>Ipilimumab</td>
<td>NR (disease-control rate 27%)</td>
<td>4.3 (median PFS 2.8 months, 1-year survival 20%)</td>
</tr>
<tr>
<td>Tazi et al</td>
<td>Retrospective (N=10) Symptomatic brain metastasis</td>
<td>Ipilimumab plus SRS</td>
<td>NR</td>
<td>16.5 (3-year OS 50%)</td>
</tr>
<tr>
<td>Falchook et al</td>
<td>Phase 1 (N=20) Asymptomatic brain metastases</td>
<td>Dabrafenib</td>
<td>4 (40%) CR and 4 (40%) PR</td>
<td>NR</td>
</tr>
<tr>
<td>Long et al</td>
<td>Phase 2 (BREAK-MB) (N=172) BRAF-mutant brain metastases</td>
<td>Dabrafenib</td>
<td>Response (CR or PR)</td>
<td>NR</td>
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<tr>
<td>Dummer et al</td>
<td>Pilot (N=24) Non-resectable and symptomatic on stable dose of steroid</td>
<td>Vemurafenib</td>
<td>16%</td>
<td>NR</td>
</tr>
<tr>
<td>Keeford et al</td>
<td>Phase 2 (N=146) Active brain metastases Cohort A: no previous local treatment (n=90); Cohort B: previous local treatment (n=56)</td>
<td>Vemurafenib</td>
<td>Cohort A: 18%. Cohort B: 20%</td>
<td>Cohort A: 6.5 (median PFS 3.7); Cohort B: 8.4 (median PFS 4.6)</td>
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<tr>
<td>Narayana et al</td>
<td>Retrospective (N=12) Brain metastases</td>
<td>Vemurafenib with concomitant or sequential WBRT, SRS, or both</td>
<td>Response (CR or PR) 75%</td>
<td>13.7</td>
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</table>

See appendix for full list of references. CR=complete response. PR=partial response. SD=stable disease. WHO=WHO criteria. ir-RC=immune-related response criteria. OS=overall survival. SRS=stereotactic radiosurgery. NR=not reported. WBRT=whole-brain radiotherapy. PFS=progression-free survival.

(95% CI 4·1–10·8), compared with 3·7 months (1·6–7·3) for patients with symptomatic brain metastases. The steroid-free cohort had a 1-year survival of 31% and 2-year survival of 26%, compared with 19% (1-year survival) and 10% (2-year survival) for patients with symptomatic brain metastases.

The US expanded-access study investigating ipilimumab in metastatic melanoma, CA184-045,\(^5\) allowed entry of patients with stable, asymptomatic brain metastases. 165 patients enrolled with brain metastases, all received 10 mg/kg of ipilimumab, and 1-year survival was reported to be 20%. Taken together, these data support that ipilimumab should be regarded as an active treatment for patients with melanoma brain metastases.

A single-arm phase 2 trial (NIBIT-M1)\(^48,49\) tested the combination of ipilimumab with fotemustine in 86 patients with metastatic melanoma, including 20 patients with asymptomatic brain metastases. 40 (47%) patients, including ten with brain metastases, achieved good disease control. For patients with brain metastases, the median immune-related progression-free survival was 4.5 months, and the median brain-specific progression-free survival was 3.0 months. Updated results of this study\(^50\) reported a 3-year survival of 28.5% for the whole study population and 27.8% for the cohort with melanoma brain metastases (seven patients lived beyond 2 years). The contribution of fotemustine in combination with ipilimumab to outcome improvement beyond 2 years). The contribution of fotemustine in combination with ipilimumab to outcome improvement beyond 2 years).

Queirolo and colleagues\(^50\) reported the outcomes of 146 patients with asymptomatic brain metastases, who received treatment with second-line ipilimumab. The median progression-free survival was 2.8 months, median overall survival was 4.3 months, and 1-year overall survival was 20% (table 4).\(^50\) A UK retrospective review of 193 previously treated patients with metastatic melanoma included 35 patients with brain metastases,
most of whom were steroid dependent. The overall survival of patients with and without brain metastases was significantly different at 1 year (34% vs 17%; p=0.0069), with some suggestion of similar results at 2 years (15% vs 13%; p=0.0069), implying that long-term outcome of patients with brain involvement is not uniform and that only a subgroup of patients is likely to benefit from ipilimumab.

The pooled analysis of phase 2 and 3 ipilimumab trials, including the phase 2 brain metastasis trial CA184-042, has shown a survival plateau of 20% starting from 3 years and extending as far as the last follow-up of 10 years. The available evidence suggests that this pattern of durable response is likely to apply to patients with responding brain metastases.

Other immune checkpoint inhibitors are being investigated, and anti-PD1 monoclonal antibodies (nivolumab and pembrolizumab) are showing the greatest promise in patients with metastatic melanoma both as single agents and in combination with ipilimumab. Although initial trials have included patients with stable brain metastases, the numbers of all patients were small, and the results for this subgroup have not been reported separately. Two phase 2 studies (CheckMate204 [NCT02320058] and ABC trial [ACTRN12614001315606]) are underway to assess the combination of nivolumab and ipilimumab in patients with melanoma brain metastases (table 1).

**BRAF-targeted agents**

*BRAF* mutations occur in up to 50% of melanomas. The common mutations are Val600Glu (V600E; 80%) and Val600Lys (V600K; 14%). Vemurafenib was the first BRAF kinase inhibitor to be licensed for treatment of BRAF-mutant metastatic melanoma on the basis of superior survival compared with standard dacarbazine. The first report of the benefit of vemurafenib for active brain metastases was in a girl aged 16 years with rapidly progressing *BRAF*<sup>V600E</sup>-positive melanoma. In a study of 24 patients with previously treated symptomatic brain metastases, vemurafenib treatment resulted in a median progression-free survival of 3–9 months (95% CI 3–0–5.5) and a median overall survival of 5.3 months (3.9–6–6). The proportion of patients with a partial response was 42–0% (95% CI 22–1–63–4) at both intracranial and extracranial sites. Of 19 patients with measurable intracranial disease, seven (37%) had an intracranial response, and the median overall survival was 46 weeks for responding patients. A retrospective study of 27 patients with *BRAF*-mutant melanoma brain metastases who received vemurafenib reported a lower intracranial response (50%) than extracranial response (71%). The median intracranial progression-free survival was 4–6 months (95% CI 2–7–7.9), and the 1–year overall survival was 30–4%. Of note, patients with a poor response to vemurafenib in this study had tumour-associated mutations in genes that activate the phosphatidylinositol 3-kinase–AKT pathway.

Dabrafenib, another BRAF inhibitor, has also shown activity in patients with melanoma brain metastases. In a phase 1 dose-escalation study, nine of ten patients with melanoma brain metastases achieved an objective response, and four of these were complete responses. The subsequent BREAK-MB phase 2 study recruited 172 patients with melanoma brain metastases who were split into two cohorts: patients who had no previous brain treatment (n=89) and patients with previous treatment (n=83). Disease control (81% vs 89%) and median overall survival (33 weeks vs 31 weeks) of both cohorts were impressive and remarkably similar (table 4). These findings were corroborated in a large Australian study, which reported similar responses in intracranial and extracranial sites (78% vs 90%) and identical median site-specific progression-free survival (24 weeks in 23 patients with melanoma brain metastases). Median progression-free survival was 16–3 weeks, and median overall survival was 36–6 weeks.

Inhibition of the MEK kinase, which acts downstream of BRAF, has also been investigated as a therapeutic target in patients with metastatic melanoma. The phase 3 METRIC trial comparing trametinib, an oral selective MEK inhibitor, with chemotherapy (intravenous dacarbazine or paclitaxel) showed a response in 22% of patients, progression-free survival of 4–8 months, and 6-month survival of 81% in patients with BRAF-mutant metastatic melanoma treated with trametinib. However, the main role for MEK inhibition seems to be in combination with BRAF inhibitors: a phase 3 trial has shown superior progression-free survival and overall survival for the combination of BRAF and MEK inhibition compared with BRAF inhibition alone. The efficacy of the combination of BRAF and MEK inhibitors in melanoma brain metastases is currently being studied in two phase 2 trials (NCT02039947 and NCT02230306; table 1).

The high proportion of patients achieving responses with BRAF-targeted drugs within weeks of starting treatment has raised the question of whether these drugs can be used effectively in the neoadjuvant setting to downstage high-volume, inoperable disease to help with surgical intervention. Disease sites of interest include bulky regional lymph nodes and brain metastases. Case reports suggest that this approach might be successfully applied to patients with brain involvement, although no formal trial has so far been launched.

The responses seen in patients with brain metastases who had been given BRAF inhibitors and MEK inhibitors are surprising because, in experimental models, these high-molecular-weight molecules with poor lipid
solubility do not penetrate an intact blood–brain barrier, calling into question the importance of the barrier.65

**Combining systemic therapies with radiotherapy**

Experiments in mice have shown that radiotherapy might have an immunomodulatory effect on CTLA-4 blockade by ipilimumab, especially when hypofractionated radiotherapy is used.66 In a retrospective series of 77 patients with melanoma brain metastases, of whom 35 received combined modality treatment, the addition of ipilimumab to SRS improved median overall survival from 4·9 months to 21·3 months (p=0·03) and 2-year overall survival from 19·7% to 47·2% compared with SRS alone (table 4).67 In a review of 33 patients with melanoma brain metastases who received ipilimumab plus WBRT or SRS,68 median overall survival was 18·3 months, compared with 5·3 months for 37 patients who received radiotherapy alone. Another series reported that ten patients with melanoma brain metastases who were given ipilimumab plus SRS had similar survival to 21 patients with melanoma without brain metastases who received ipilimumab alone.69 However, in a non-randomised study of 58 patients with limited melanoma brain metastases who had undergone SRS, the addition of ipilimumab did not improve survival (6-month overall survival was 46% with SRS alone vs 56% with combined treatment; p value was non-significant),70 a retrospective study71 also did not find any survival benefit with the addition of ipilimumab to SRS.

Importantly, radionecrosis of the brain might result when ipilimumab is combined with radiation. One study72 suggested that around 10% of patients given ipilimumab in combination with focal radiotherapy or WBRT might be at risk, with peak incidence around 12–15 months after radiation. In another study of 34 patients with melanoma brain metastases given ipilimumab with radiotherapy,73 radionecrosis of the brain occurred in 11 (41%) of 27 patients who had undergone SRS with or without WBRT, and was not reported in patients who received only WBRT (n=7). This incidence is higher than that after radiotherapy for primary brain tumours. Patients with melanoma brain metastases present with a range of neurological symptoms, and the differential between malignant progression and radionecrosis of the brain is not straightforward.

Activation of an antitumour immune response after radiotherapy-induced cell death can lead to regression of tumours at non-irradiated sites (known as the abscopal effect).74 Several studies have reported abscopal effects when radiotherapy is combined with anti-CTLA-4 inhibitors in patients with melanoma.75 However, whether the abscopal effect can lead to regression of melanoma brain metastases is unknown.

The benefits and risks of the combination of radiotherapy with BRAF-targeted agents are also yet to be established. A study of 12 patients with melanoma brain metastases who were given vemurafenib either before (n=7) or concurrently with (n=5) radiosurgery or WBRT76 reported a 6-month overall survival of 92%, with a radiological response of 75%, including 48% of patients with a complete response. An in-vitro study reported that vemurafenib sensitises melanoma cells to radiation,15 possibly owing to an increase in residual radiation-induced double-strand DNA breaks. Increased toxicity after radiotherapy, including both acute reactions and radiation recall, has been reported in patients receiving vemurafenib.77 Although the evidence base is still small, dosing of BRAF inhibitors is generally interrupted briefly if radiotherapy is being given.

Whether a combination strategy of systemic and radiotherapy will translate to clinical benefit needs to be investigated prospectively. Some studies are underway (table 1), although very few are randomised. However, many issues need to be assessed, such as the sequence of radiation and systemic therapy, radiation fractionation, dosing of both radiotherapy and systemic agents, and identification of potential markers of response to individualise treatment.

**Brain metastases from melanoma of unknown primary site**

Around 3% of patients present with melanoma of unknown primary site. Since most studies on this type of melanoma include brain metastases along with non-nodal clinical presentation, the true incidence of brain-only metastases is not known. The management of brain metastases from melanoma of unknown primary site is similar to that from a known primary site and depends on the KPS and the number, size, and location of metastases (figure 2).78

**Primary leptomeningeal melanotic tumours**

Primary leptomeningeal melanotic tumours occur as melanocytoma (low-grade and intermediate-grade tumours) and melanoma (high-grade tumours). Melanocytomas usually occur in the spinal region and melanomas in the subtentorial region. Typical radiological appearance is that of a solitary so-called melanotic brain metastasis, and metastasis from a cutaneous melanoma must be ruled out. Complete surgical excision is the treatment of choice. In patients with incomplete resection, adjuvant radiotherapy could be considered.79 Patients with completely excised primary leptomeningeal melanoma have a good prognosis, whereas patients who present or recur with diffuse leptomeningeal disease have a poor prognosis.80

**Conclusions**

Development of brain metastases and treatment resistance are key obstacles in improving the survival of patients with advanced melanoma. In selected patients with limited brain involvement, the possibility of
long-term control by use of surgery or SRS should be considered. The role of WBRT after local intervention in oligometastatic melanoma brain metastases has yet to be defined. However, surgery or SRS is likely to be an option only in at best a third of patients with melanoma brain metastases, since most patients present with more extensive brain involvement. For these patients, WBRT has traditionally been offered as a palliative measure.

Modern systemic therapies for metastatic melanoma have proven effective even when no brain involvement exists. For patients with BRAF-mutant melanoma, BRAF-targeted agents could be used preferentially to radiotherapy while the potential benefits and risks of the combination of radiotherapy and immunotherapy are still being studied (figure 2).

Most studies have used various surrogate endpoints (eg, local control and out-of-field failure) of clinical efficacy, which makes comparisons and interpretation of the clinical benefits of existing treatment options difficult. Therefore, an urgent need exists to establish an international consensus on the appropriate clinical endpoints to compare various treatments for melanoma brain metastases. Ideal endpoints of clinical efficacy should include assessment of symptom control, neurocognitive functions, cranial disease-free interval, and overall survival. Although formal prospective studies are needed to guide future clinical management, all patients with melanoma brain metastases should be discussed in specialist multidisciplinary team meetings, taking into account expert advice from neurosurgeons, radiation oncologists, and melanoma specialist oncologists, to select the best possible treatment and encourage participation in research.

Contributors

TA conceived this Review and wrote the first draft. All authors contributed to critical review of literature and writing of successive drafts, and approved the final manuscript.

Declaration of interests
KF has attended advisory boards for Roche. PC has attended advisory boards and undertaken ad-hoc consultancy for Bristol-Myers Squibb, Roche, GlaxoSmithKline, Novartis, and Merck, and received research funding from Roche. SJ has undertaken ad-hoc consultancy for Roche and Bayer. TA and CP declare no competing interests.

References


