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Management of intracranial melanomas in the era of precision medicine

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ABSTRACT

Melanoma is the most lethal of skin cancers, in part because of its proclivity for rapid and distant metastasis. It is also potentially the most neurotropic cancer in terms of probability of CNS metastasis from the primary lesion. Despite surgical resection and radiotherapy, prognosis remains guarded for patients with brain metastases. Over the past five years, a new domain of personalized therapy has emerged for advanced melanoma patients with the introduction of BRAF and other MAP kinase pathway inhibitors, immunotherapy, and combinatory therapeutic strategies. By targeting critical cellular signaling pathways and unleashing the adaptive immune response against tumor antigens, a subset of melanoma patients have demonstrated remarkable responses to these treatments. Over time, acquired resistance to these modalities inexorably develops, providing new challenges to overcome. We review the rapidly evolving terrain for intracranial melanoma treatment, address likely and potential mechanisms of resistance, as well as evaluate promising future therapeutic approaches currently under clinical investigation.

INTRODUCTION

Melanoma comprises 4% of all skin cancers but is responsible for 80% of skin cancer-related deaths [1], in part because of its proclivity for metastasis [2]. Once disseminated, median overall survival averages 6–11 months [3, 4]; overall survival is reduced to 4–5 months for metastases to the brain [5–7]. Until the last five years, treatment options for melanomas that have metastasized to the brain have been limited. Despite surgical resection and irradiation, a majority of patients experience rapid disease progression [8]. Minimal benefit has been observed with cytotoxic chemotherapy [9].

Recently, developments in molecular and immunological targeting have produced new therapeutics which have changed the landscape of melanoma treatment and prognosis. This review examines recent developments in targeted systemic treatment of advanced melanoma—including BRAF inhibitors, MEK pathway inhibitors, the blockade of the CTLA-4 and PD-1/PD-L1 immune checkpoints, and other novel anti-neoplastic agents—and highlight lessons learned from countering acquired resistance.

Epidemiology of intracranial melanomas

Melanoma is currently the sixth most common cancer in the United States, with the highest rate of untreated fatality among cutaneous malignancies [1]. Its rate of diagnosis is increasing more quickly than any other cancer in the nation, partially because of escalated sun-seeking behavior in previous decades, greater community...
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with significant reduction in local recurrence [23–25], by whole brain radiation therapy is classically associated disease Surgery and/or SRS for single or oligo metastatic exhibits limited efficacy. Conventional chemotherapy in the form of effects on overall survival even in the presence of local employed as first-line treatments, but exert only modest melanoma. Surgery and irradiation are commonly considered a challenge for the management of malignant melanoma, adjuvant to surgery/SRS may reduce local recurrence in patients with metastatic melanoma, but does not necessarily improve overall survival [31], although higher doses of WBRT increases median survival from 13 months to 17 months [32]. In addition, the use of fractionated WBRT after resection (as opposed to focal or stereotactic radiosurgery) has been challenged due to high melanoma radiore sistance rates [33] and associated complications such as radiation leukoencephalopathy, edema, and cognitive decline [34]. SRS plus WBRT may result in equivalent or better survival compared with surgery and WBRT alone, although the survival advantage remains modest [23, 35].

Palliative WBRT

Of note, primary administration of WBRT (e.g., 30 Gy administered in 10 fractions) may be provided to patients who are not resection candidates due to location or number of metastases as a palliative measure. Median survival in these cohorts has been reported to increase from 2.1 months to 3.6- 4.8 months [7, 36–38].

Conventional chemotherapies have been utilized for patients with extensive disease burden with limited success. Dacarbazine was the first FDA-approved chemotherapy for melanoma, but conferred an overall response rate of only 10–20%, with less than 5% complete response [39–41] and mean survival of less than 8 months [42, 43]. Lack of efficacy has been attributed to an inability to transverse the blood-brain barrier (BBB) and the activity of efflux pumps such as breast cancer resistance protein and P-glycoprotein [44]. Fotemustine, a nitrosourea capable of crossing the BBB [45], subsequently

Conventional therapies for intracranial melanoma

The high rate of intracranial metastasis presents a considerable challenge for the management of malignant melanoma. Surgery and irradiation are commonly employed as first-line treatments, but exert only modest effects on overall survival even in the presence of local control. Conventional chemotherapy in the form of alkylating agents (dacarbazine, temozolomide) also exhibits limited efficacy.

Surgery and/or SRS for single or oligo metastatic disease

Resection of solitary or oligo-metastases followed by whole brain radiation therapy is classically associated with significant reduction in local recurrence [23–25], although the presence of multiple lesions confers poorer prognosis [26]. Even in the setting of multiple metastases, however, a lesion causing significant mass effect and neurologic compromise or near eloquent regions of the brain may be candidate for resection.

Stereotactic radiosurgery (SRS), independently or as adjuvant therapy to the resection cavity following surgery, has shown some efficacy in controlling multiple intracranial tumors, with optimal treatment ranges between 10 and 20 Gy [27]. Indications include tumors that are smaller than 3 cm, in deep locations, without significantly associated edema, midline shift, or hydrocephalus, and relatively good prognosis. Tumor control rates with SRS alone have been reported to range from 40% to 75% [28–30], with a median survival of 8–10 months following initial diagnosis.

WBRT as an adjunct to surgery/SRS

Adjuvant whole brain radiation therapy (WBRT) may reduce local recurrence in patients with metastatic melanoma, but not necessarily improve overall survival [31], although higher doses of WBRT increases median survival from 13 months to 17 months [32]. In addition, the use of fractionated WBRT after resection (as opposed to focal or stereotactic radiosurgery) has been challenged due to high melanoma radiore sistance rates [33] and associated complications such as radiation leukoencephalopathy, edema, and cognitive decline [34]. SRS plus WBRT may result in equivalent or better survival compared with surgery and WBRT alone, although the survival advantage remains modest [23, 35].

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demonstrated marginally improved median progression-free survival (PFS) by 1–2 months relative to dacarbazine, with response rates of 5–6% [46, 47].

Temozolamide is a well-tolerated systemic therapy that does not significantly improve objective response rate and progression free survival as a single agent, but may be promising in combination therapy with other drugs [48]. Recent phase 1/2 preliminary data for decitabine—a DNA methyltransferase inhibitor attenuating CpG methylation in metastatic melanoma—in combination with temozolamide indicated an overall response rate of 18% and a median overall survival of 12.4 months [49].

Prophylactic chemoprevention has shown reasonable success in several studies for cancers other than melanoma [50]. In the case of melanoma, as metastases employ integrin signaling to grow along blood vessels, future approaches may opt to administer integrin inhibiting agents (e.g., cilengitide) during early disease progression to delay intracranial colonization [51]. In practice, however, cancer chemoprevention is seldom utilized in the clinical setting [52].

**Limits of conventional therapies**

To date, conventional treatment options have provided limited strategies to target metastatic melanoma. Surgical resection and irradiation are often not feasible in many melanoma cases due to the multiplicity of intracranial metastases and their relative radioresistance. With emerging understanding of tumor heterogeneity across space and time [53], melanoma brain metastases also likely represent diverse entities with varying sensitivities to treatment and ready acquisition of resistance. Recurrent disease and progressive metastases further thwart the effectiveness of systemic therapies. In this backdrop, the advent of targeted therapies for metastatic melanoma in the past 5 years has offered renewed promise.

**Mechanisms of melanoma metastasis to the brain**

The identification of actionable mechanisms of metastasis in any cancer type remains a “holy grail” of cancer research, as disease dissemination is the main driver of mortality. Although much remains to be learned in our understanding of how melanoma cells metastasize to the brain, a number of mechanisms are likely to contribute to this process.

**Cerebral chemotaxis**

Melanoma metastasis is facilitated by the well-perfused dermal capillary and lymphatic network at its site of origin [54]. A combination of autocrine and paracrine factors influence melanoma chemotaxis and survival in the brain [55–57]. Melanoma cells express low-affinity neurotrophin receptors p75NTR and TrKc, which are positively regulated by nerve growth factor (NGF) and neurophin-3 (NT-3), leading to enhanced production of extracellular matrix (ECM) degradative enzymes such as heparanase and culminating in the breakdown of the blood-brain barrier (BBB). Chemokines and their receptors are also implicated in preferential homing of melanoma cells to target sites, including CXC chemokine receptor 4 (CXCR-4) and C-C chemokine receptor 7 (CCR-7) [58]. Recently, expression of the protein PLEKHA5 has been demonstrated to be higher in cerebrotropic metastases compared to systemic melanomas, suggesting an additional biomolecular target for future study [59].

**Cytokine signaling**

Paracrine cytokine signaling by activated astrocytes and microglia may further stimulate tumor development. Vascular endothelial growth factor A (VEGF-A) and IL-6, in particular, promote accelerated growth and infiltration of melanoma cell lines in vitro with accompanying co-optation of peritumoral vessels and increased vascular permeability [60]. VEGF expression in melanoma metastases can be upregulated by loss of suppressor of cytokine signaling-1 and ensuing activation of signal transducer and activator of transcription 3 (STAT3) [61]. Other upregulated genes in advanced intracranial melanoma include angiopoietin-like protein 4, cyclooxygenase-2 (COX-2), and matrix-metalloproteinase-1 (MMP-1) [55].

**Immune evasion**

After seeding the CNS, melanoma metastases are subject to the unique immunologic environment provided by the brain. Interestingly, murine and human tumor cells have been shown to lose normal expression of the tumor suppressor PTEN after metastasis to the brain, but not to other organs, which is then reinstated after leaving the CNS environment. The mechanism of plasticity is postulated to be produced by astrocyte-dependent, epigenetically regulated protein downregulation, where astrocyte-derived exosomes arbitrate an intercellular exchange of PTEN-targeting microRNAs to metastatic tumor cells, while depletion of these microRNAs or blockade of astrocyte exosome secretion effectively “rescues” PTEN expression and suppresses brain metastasis [62].

In contrast to the historic view of the CNS as an immunologically privileged compartment, bounded by the blood-brain barrier, research increasingly reveals that CNS antigens are in fact accessible to peripheral lymphoid tissues and able to mount significant antitumoral immunity [63–65]. Furthermore, the number of intratumoral lymphocytes positively correlates with increased patient survival; metastatic melanoma patients
with brisk lymphocyte activity demonstrated 1.5–3 times longer overall survival compared to those without, although this was not a brain-specific finding [66, 67]. Recently, a functional lymphatic network abutting the dural sinuses was identified that provides an anatomic conduit for immune cell influx and efflux to the CNS [68, 69]. Taken together, these data suggest that immune potentiation may be a potent strategy for targeting CNS metastases.

Molecularly targeted therapies for melanoma

In 2011, the treatment of metastatic melanomas was revolutionized by FDA approval of two new agents: vemurafenib (Zelboraf®; Genentech, San Francisco, California, USA) and ipilimumab (Yervoy™; Merck, Kenilworth, New Jersey, USA). Both address critical and independent pathways of advanced melanoma growth: the mitogen-activated protein (MAP) kinase signaling pathway for vemurafenib [70, 71] and the CTLA-4 signaling pathway for ipilimumab [72, 73]. These new therapies heralded a paradigm shift by providing rational targeted therapies for a disease with a poor prior history of treatment (Table 1).

Role of BRAF mutations in melanoma malignancy

Mutations in BRAF are the most common targetable genetic variant in advanced melanoma [74]. BRAF mutations are found in 40–60% of melanomas, with a valine to glutamic acid substitution at residue 600 (V600E) as the most common variant (75–80%), followed by substitution to lysine (V600K, 17–22%) and arginine (V600R, 3–4%) [75, 76]. Differences in BRAF genetic variants (V600E vs. other mutations) appear to be dependent on patient demographics and primary disease site, with non-V600E tumors occurring more frequently in men, older patients, and truncal lesions [77, 78]. Tumors with non-V600E mutations also have a shorter disease-free interval from diagnosis of primary melanoma to first distant metastasis compared to their V600E counterparts [78]. Prognosis is less favorable for non-V600E mutations as efficacy of targeted therapy is more limited [78].

Raf exists in three mammalian isoforms: ARAF, BRAF, and CRAF (also known as Raf-1), of which the latter two are proto-oncogenic. Mutant BRAF triggers constitutive activation of the MAPK/ERK pathway and is typically mutually exclusive of activating RAS mutations in tumors [74, 79]. Other BRAF-mediated mechanisms in melanoma include UV activation of BRAF-driven tumorigenesis through single nucleotide mutations in TP53 [80] and copper-promoted MEK1 phosphorylation of ERK [81]. Co-occurrence with telomerase reverse transcriptase (TERT) promoter mutations (found in 38% of melanomas) was observed to be more commonly associated with high-risk clinicopathologic characteristics [82], suggesting potential interplay of TERT promoter and BRAF mutations in melanoma evolution.

BRAF inhibitors for invasive melanoma

Vemurafenib is an inhibitor of the BRAF serine threonine kinase mutant and blocks its constitutive activation of the MAPK mitogenic signaling pathway. A phase 2, multi-center study of vemurafenib in 132 previously treated BRAFV600E mutant metastatic melanoma patients showed a response rate of 53%, a median duration of response of 6.7 months, and a median overall survival of 15.9 months [83]. Interim analysis during a phase 3 randomization of 675 previously untreated BRAFV600E mutant metastatic melanoma patients to vemurafenib or dacarbazine revealed significant benefit for the vemurafenib cohort; 80% of patients showed a reduction in tumor size, with over half showing a reduction of > 30% [71, 84]. Median overall survival (OS) and PFS both increased by 4–5 months in the vemurafenib arm.

Most initial clinical trials excluded patients with metastases to the CNS, unless such metastases had been definitively treated with no signs of progression or need for glucocorticoid therapy for 3 months or more prior to initiation of treatment [71]. Nevertheless, isolated reports emerged suggesting positive effects of vemurafenib in controlling growth and reducing mass effect for intracranial melanoma metastases [71, 84]. Median overall survival (OS) and PFS both increased by 4–5 months in the vemurafenib arm.

A phase 2, multi-center study of vemurafenib in 132 previously untreated patients with active brain metastases who were treated with vemurafenib, this suggests that vemurafenib monotherapy may be insufficient for intracranial metastatic melanoma [87]. A phase 2 study evaluating vemurafenib in a larger group of BRAF-mutant patients with active brain metastases is currently underway (NCT01378975).

In recognition of the potential of BRAF inhibition, dabrafenib (Tafinlar®; Novartis, Mission Viejo, California, USA) has also been FDA-approved. Drug efficacy was demonstrated in patients with active brain metastases, something that was not originally evaluated for vemurafenib [88]. In a phase 2 trial of BRAFV600E or
<table>
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<tr>
<th>Drug Name</th>
<th>Mechanism</th>
<th>Target tumor population</th>
<th>FDA Approval Date</th>
<th>FDA Recommended Administration Protocol</th>
<th>Response Rate</th>
<th>Side Effects</th>
<th>Resistance Onset</th>
<th>Treatment options after onset of resistance</th>
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<td>Molecular Targets</td>
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<tr>
<td>Vemurafenib (Zelboraf®)</td>
<td>BRAF V600E/K inhibitor</td>
<td>BRAF V600E/K mutant</td>
<td>August 2011</td>
<td>960 mg 2x daily</td>
<td>30–39%, in intracranial patients6; 40</td>
<td>Novel primary malignancies, tumor promotion in BRAF wild-type patients, hypersensitivity reactions, dermatologic reactions, QT prolongation, hepatotoxicity, photosensitivity, ophthalmologic reactions94–96.</td>
<td>7 months, frequent69–71</td>
<td>Anti-BRAF/MEK co-therapy, dual Ras-Mek-Erk/PI3K-PKB inhibition, ERKi, intermittent dosing, combination of BRAFi with immunotherapies (e.g., anti-CTLA, anti-PD1, anti-PD-L1)109–117, 119, 123–126</td>
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<td>Dabrafenib (Tafinlar®)</td>
<td>BRAF V600E/K inhibitor</td>
<td>BRAF V600E/K mutant</td>
<td>May 2013</td>
<td>150 mg 2x daily</td>
<td>31–52%, in intracranial patients6; 40</td>
<td>Novel primary malignancies, tumor promotion in BRAF wild-type patients, hemorrhage, venous thromboembolism, cardiomyopathy, ocular toxicities, febrile reactions, skin toxicity, hyperglycemia, glucose-6-phosphate dehydrogenase deficiency94–96.</td>
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<tr>
<td>Trametinib (Mekinist™)</td>
<td>MEK inhibitor</td>
<td>BRAF V600E/K mutant</td>
<td>January 2014</td>
<td>2 mg 1x daily</td>
<td>54%60</td>
<td>Novel primary malignancies, tumor promotion in BRAF wild-type patients, hemorrhage, venous thromboembolism, cardiomyopathy, ocular toxicities, interstitial lung disease, skin toxicity, febrile reactions, hyperglycemia15.</td>
<td>9.9 months, frequent61</td>
<td></td>
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<tr>
<td>Cobimetinib (Cotellic®)</td>
<td>MEK inhibitor</td>
<td>BRAF V600E/K mutant</td>
<td>November 2015</td>
<td>60 mg 1x daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity, in combination with vemurafenib</td>
<td>68%62</td>
<td>Central serous retinopathy, gastrointestinal events, photosensitivity, elevated aminotransferase levels, and an increased creatine kinase level15.</td>
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<td>Immunotherapy</td>
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<tr>
<td>Ipilimumab (Yervoy®)</td>
<td>CTLA-4 inhibitor</td>
<td>Unrestricted</td>
<td>March 2011</td>
<td>3 mg/kg administered intravenously every 3 weeks</td>
<td>15–30%, in intracranial patients6; 45</td>
<td>Immune-mediated enterocolitis, immune-mediated hepatitis, immune-mediated dermatitis, immune-mediated neuropathies, immune-mediated endocrinopathies98, 136.</td>
<td>&gt; 1 year, rare61</td>
<td>Other immunotherapies, histone-deacetylase inhibition, indomethacin, ACT, combination SRS and immunotherapy99–101</td>
</tr>
<tr>
<td>Nivolumab (Opdivo®)</td>
<td>PD-1 inhibitor</td>
<td>Unrestricted</td>
<td>December 2014</td>
<td>3 mg/kg administered intravenously every 2 weeks</td>
<td>28%155</td>
<td>Immune-mediated pneumonia, immune-mediated colitis, immune-mediated hepatitis, immune-mediated nephritis and renal dysfunction, immune-mediated hypothyroidism and hyperthyroidism15.</td>
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<tr>
<td>Pembrolizumab (Keytruda®)</td>
<td>PD-1 inhibitor</td>
<td>Unrestricted</td>
<td>September 2014</td>
<td>2 mg/kg administered intravenously every 3 weeks</td>
<td>37–38%154</td>
<td>Immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated hypophysitis, immune-mediated nephritis and renal dysfunction, immune-mediated hypothyroidism and hyperthyroidism15.</td>
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**BRAFV600E** mutant melanoma metastases to the brain, 39% of previously untreated **BRAFV600E** patients demonstrated a response while 31% of **BRAFV600E** patients with disease progression following prior surgery or radiation therapy also demonstrated a response. Median OS was 31–33 weeks for patients with **BRAFV600E** metastases, as compared to 16–22 weeks for those with **BRAFV600K** mutant tumors; PFS was 16 weeks for **BRAFV600E** patients and 8–16 weeks for **BRAFV600K** patients, depending on prior treatment status [88]. A phase 3 randomized trial for dabrafenib in 250 patients with V600E-mutant stage III or IV melanoma showed a 50% response rate and an improved PFS over dacarbazine (5.1 vs. 2.7 months) [89].

**Blood barrier efficacy for BRAF inhibitors**

Although the mechanism of blood-brain transport is unclear, the response and improved survival curves in patients treated with BRAF inhibitors suggest some level of inhibitor penetration in patients with active cranial melanoma metastases [86, 90]. It serves to note that a range of factors may play a role in penetrance efficacy, including the number and size of brain metastases, the presence of co-morbidities, neurological complications, and tumor mutation status [73, 91].

In animal studies, BRAF inhibitors have been shown to be substrates for barrier efflux pumps, with increases up to 10-fold in brain distribution for P-glycoprotein and breast cancer resistance protein-1 knockouts [92]. Greater CNS penetration is observed for dabrafenib than for vemurafenib under similar dosing schedules [93]. Development of delivery mechanisms inhibiting the activity of efflux transporters may further increase the therapeutic efficacy of BRAF inhibition in intracranial disease.

**Side effects of BRAF inhibition**

Long-term administration of BRAF inhibitors has been observed to associate with a range of skin changes, febrile reactions, arthralgia, headache, venous thromboembolism, cardiomyopathy, and hyperglycemia [94]. More concerning, secondary malignancies including squamous cell carcinomas, secondary melanomas, and recurrence of pre-existing malignancies have also been reported [95, 96]. These are predominantly attributed to MAPK pathway activation and increased Ras activity in BRAF wild-type cells exposed to BRAF inhibitors [97], adding a cautionary note to avoid BRAF inhibitor therapy in melanoma patients without mutant **BRAF** status.

**MEK inhibition**

The presence of **BRAF** mutation is also associated with enhanced and selective sensitivity to MEK inhibition in melanoma cells [98]. Concomitant with the development of BRAF inhibitors, several MEK inhibitors—including trametinib, selumetinib, and binimetinib [99]—have emerged in recent years, adding to the existing pharmacologic armamentarium.

Trametinib (Mekinist™; Novartis, Mission Viejo, California, USA), a MEK 1/2 inhibitor, has shown therapeutic promise as either a monotherapy for **BRAF**-mutant melanoma or in combination with dabrafenib. A phase 3 trial comparing trametinib to dacarbazine or paclitaxel in metastatic **BRAFV600E**-mutant melanoma patients demonstrated significant improvement in median PFS and a 6-month survival rate of 81% despite a 47% crossover rate from the chemotherapy group [100]. Of note, only 4% of the patients receiving trametinib harbored a known brain metastasis at study enrollment. Combination therapy with dabrafenib or cobimetinib results in markedly improved response, with median PFS in phase 3 studies ranging from 9.3–9.9 months for combination treatment versus 8.8 months for dabrafenib alone [101] and 6.2 months for cobimetinib alone [102]. Although these studies did not include patients with brain lesions, a number of phase 2 studies (COMBI-MB, co-BRIM3, NCT01978236) are currently investigating the effect of BRAF/MEK inhibitory therapy on active brain metastasis.

Cobimetinib (Cotellic®; Genentech, San Francisco, California, USA), another MEK inhibitor, appears to have a favorable profile when combined with vemurafenib in patients with advanced **BRAF**-mutant melanoma. Progression-free survival during a multi-center phase 3 study was reported to reach 9.9 months in the combination group (vemurafenib + cobimetinib) and only 6.2 months in the control group (vemurafenib alone) [102]. Response rate in the combination arm was 68% versus 45% (control), with respective complete response rates of 10% and 4%. Vemurafenib and cobimetinib administered in combination was associated with some increase in toxicity, with rash, diarrhea, photosensitivity, and hepatic-enzyme abnormalities as adverse events. Incidence of secondary cutaneous cancers decreased with combination treatment. Patients with brain metastases were allowed to enroll so long as the lesion had been inactive for ≥3 weeks.

As with BRAF inhibition, the CNS penetrance of MEK inhibition is unclear, although animal models suggest restriction by barrier efflux pumps [103]. Given that clinical trials have not included a substantial number of patients with brain metastases, future directions may include the exclusive testing of a CNS disease cohort to better evaluate blood brain barrier efficacy.

**Acquired resistance to BRAF and MEK inhibition**

One major drawback to BRAF inhibition is a rapid onset of resistance, with average time to acquired resistance to kinase inhibition being less than 7 months [104]. A majority of currently recognized resistance mechanisms culminate in Ras-Raf-MEK-ERK pathway
reactivation (Figure 2), mutation of downstream \textit{MEKI} (also known as \textit{MAP2K1}) kinase [105], activating mutations of neuroblastoma viral RAS oncogene homolog (\textit{NRAS}) [106] and \textit{KRAS} [107], and dimerization of alternatively spliced BRAF [108]. \textit{BRAF}\textsuperscript{V600E} copy number amplification (observed in 8–20% of resistant melanoma samples) [107, 109] and elevated \textit{CRAF} transcription [110] can also re-instigate ERK phosphorylation. Activating MEK mutations are found in less than 15% of cases, with only a subset capable of driving resistance to BRAF inhibitors [109].

ERK-independent pathways are also implicated, including the PI3K-protein kinase B (PKB)-mechanistic target of rapamycin (mTOR) pathway and the caspase-dependent apoptotic cascade. These pathways converge at formation of eukaryotic translation initiation complex 4F (eIF4F), which confers resistance to inhibition of BRAF [111]. Platelet-derived growth factor receptor β (PDGFRβ) initiation of survival pathways auxiliary to MAPK [106] and EGFR upregulation have also been observed after development of resistance [112]. In addition, BRAF inhibitors may be subject to extrusion via efflux pumps expressed by blood-brain-barrier epitheliocytes [92], allowing increased transporter expression to provide a supplementary route for intracranial BRAF inhibitor resistance.

Multiple mechanisms of resistance can develop simultaneously. In an analysis of 100 resistant melanoma samples from 44 patients, 70% of tumors demonstrated a MAPK alteration and 22% demonstrated a PI3K-PKB alteration, with 20% of patients harboring at least two distinct mechanisms of resistance [107]. Awareness of such intratumoral heterogeneity may help steer strategies for countering acquired resistance to inhibitor therapy [109].

**Overcoming BRAF and MEK inhibitor resistance**

One strategy for countering resistance is to concurrently target multiple oncogenic pathway members. A phase 2 study comparing combination therapy with dabrafenib and trametinib to dabrafenib monotherapy

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\textbf{Figure 1: Canonical MAP kinase signaling mediates critical cellular processes implicated in proliferation, differentiation, survival, and angiogenesis.} BRAF inhibitors (vemurafenib and dabrafenib) and MEK inhibitors (trametinib, selumitinib, and binimetinib) target the MAP kinase pathway to check tumor growth.
observed an unprecedented overall survival rate of 23.8 months in the co-therapy group [113]. Phase 3 comparison of dabrafenib/trametinib versus dabrafenib alone corroborated a slightly improved PFS with combination treatment (9.3 vs. 8.8 months) [114]. Notably, combination therapy was associated with a lower rate of cutaneous squamous cell carcinoma and hyperkeratoses compared to monotherapy inhibition, although higher rates of severe grade pyrexia were observed [114]. Patients with CNS dissemination were not included in these studies; the effect of BRAF/MEK inhibitor therapy on brain metastases is presently being investigated in phase 2 trials (NCT02039947, NCT02230306).

In comparison, sequential administration of a single-agent MEK inhibitor following acquired dabrafenib or vemurafenib resistance has proven largely unfruitful. A phase 2 study of trametinib in BRAF inhibitor-naive patients versus those previously treated with dabrafenib or vemurafenib demonstrated response rates only in the drug-naïve arm (25% vs. 0%; patients with active brain metastases excluded) [115]. This likely results from multiple factors, including tumor heterogeneity among patients, cross-resistance between BRAF and MEK, and the activation of alternative signaling pathways [107, 109, 116]. Interestingly, a phase 1/2 study evaluating dabrafenib/trametinib co-therapy following dabrafenib resistance showed response rates of 13% (enrollment included patients with > 3 month history of stable brain involvement); an additional 44% experienced disease stabilization of ≥ 8 weeks [117]. Patients receiving dabrafenib monotherapy for greater than 6 months before progression and subsequent co-therapy had a greater PFS compared to those with early progression after less than 6 months of monotherapy (3.9 vs. 1.8 months). This indicates a potential role for combination therapy after acquired resistance, although effect sizes appear to be modest.

Figure 2: Mechanisms and pathways of acquired resistance following BRAF inhibitor therapy.
Inhibition of ERK, further down the MAPK cascade, may offer additional benefit. ERK inhibition in vitro is more effective than MEK inhibition in the background of Ras mutations, MEK mutations, and BRAF amplification [118, 119]. As ERK belongs to the same pathway as BRAF, however, inhibition may have limited efficacy following resistance and may actually promote relief of ERK-driven negative feedback on Ras signaling [120].

Emerging evidence indicates that resistance to BRAF inhibitors confers cross-resistance to MEK inhibitors, and that targeting a single pathway may not be enough for long-term disease control [116]. In addition, suppression of either Raf-MEK-ERK or PI3K-PKB signaling leads to greater activation of the alternate pathway, suggesting that inhibition of both pathways is necessary for response durability [121]. Preliminary clinical trials assessing dual pathway inhibition are currently underway [122].

An empirical model has also proposed a role for “drug holidays” in countering acquired resistance. A proportion of cells expressing mutant or amplified BRAF become dependent on BRAF inhibition for a selective advantage, and cessation of drug administration leads to tumor regression; a staggered regimen has been shown to delay onset of resistance in both mice and human xenograft cell lines [123]. Subsequent studies investigating aberrantly spliced BRAF showed greater rates of proliferation in the presence of PLX4720 (a next-generation BRAF inhibitor) and increased sensitivity to BRAF inhibition after a period of cessation [124]. Reversal of acquired EGFR expression has also been observed in resistant cell lines after interruption of therapy [112]. Preliminary anecdotal evidence suggests that sensitivity can be re-acquired following treatment intermission [125, 126]. A phase 2 trial is underway to evaluate long-term efficacy of intermittent dosing (2 weeks on, 2 weeks off) of BRAF inhibitor LGX818 in patients with BRAF mutant metastatic melanoma (NCT01894672).

Additional strategies to overcome resistance include combination of MAPK pathway inhibitors with immunotherapies. This arrangement is currently being evaluated in a phase 1 study with BRAF\textsuperscript{V600} mutant advanced melanomas [127]. Other strategies combining targeted therapies and immunotherapies with anti-programmed cell death protein 1 (PD-1) are also in development, as are studies of programmed death ligand 1 (PD-L1) checkpoint inhibitors [128]. Therapies combining BRAF inhibitor PLX4720 and anti-CCR2 or agonistic anti-CD137 antibodies have also shown significant antitumor activity in murine transplant and tumorigenesis models [129, 130].

Immunotherapy for metastatic melanoma

Immunotherapy represents one of the most dramatic advances in cancer therapy over the last 5 years, and the treatment of melanoma has unquestionably been at the forefront of this revolution. An integrated immune response involving both innate and adaptive compartments is responsible for countering malignancy by activating T-cells into an effector state in a two stage process [64] (Figure 3). First, naïve T cells must recognize tumor-specific antigens presented by the MHC molecules on antigen presenting cells in secondary lymphoid tissue. The securement of antigen and its presentation to T cells is the definitive step in the afferent pathway of the immune response. Second, a costimulatory signal completes the activation, which is negatively regulated by several inhibitory molecules expressed on T cells, antigen presenting cells (APC), and tumor cells [131]. These antagonist signals are known as immune checkpoints and include cytotoxic T-lymphocyte antigen-4 (CTLA-4), an inhibitory receptor on lymphocytes which acts in the early priming phase of the immune response. The subsequent efferent pathway of adaptive immunity involves activated T cells homing to the tumor environment, where the PD-1/PD-L1 receptor-ligand pair acts to dampen peripheral immune activity (Figure 4). Melanomas are capable of inciting robust immune responses, making immunotherapy options particularly relevant. Despite instigating a heavy T-cell response, however, a proportion of the total CD8+ T cells in melanoma patients are functionally unresponsive to molecularly targeted drugs that can be foiled by newly acquired mutations [134, 135].

Recent experience with immune checkpoint inhibitors has resulted in impressively durable responses in a subset of patients, in comparison to higher response rates achieved with MAPK pathway inhibition that are often less durable [133]. This may potentially be explained by the plasticity of the immune response, allowing for adaptation to an evolving tumor, as opposed to molecularly targeted drugs that can be foiled by newly acquired mutations [134, 135].

Of note, although many of the novel immunotherapeutic agents cannot cross the blood-brain barrier, CD8+ cytotoxic T cells appear to be able to travel to the brain and mount a significant anti-tumor immune response [136, 137]. Supporting this evidence, recent findings have suggested an extensive dural lymphatic system that is capable of carrying both CSF and immune cells into the murine brain; further support for this system in humans remains to be demonstrated [68].

CTLA-4 inhibition

In cases of malignancy, as first shown by James Allison [138], CTLA-4 operates mechanistically by outcompeting the T-cell costimulatory molecule, CD28, for
binding to the antigen-presenting cell expressed activation ligands, CD80/CD86 (Figure 4A), which impairs cytolytic T-cell lymphocyte activation and clonal expansion [139], inhibition of helper T-cell activity, and enhancement of the immunosuppressive activity of regulatory T-cell units [140]. Inhibition of CTLA-4 leads to significantly increased immune recognition of tumor cells [141]. In patients with advanced melanoma, CTLA-4 inhibition has been observed to produce durable response rates in approximately a quarter of treated patients [142, 143].

In 2011, the FDA approved ipilimumab (Yervoy™), a human immunoglobulin (IgG1) antibody that binds and sequesters CTLA-4 with high affinity for treatment of unresectable or metastatic melanoma (Figure 4B). Ipilimumab significantly improved median overall survival for metastatic melanoma (10.1 vs. 6.4 months for control) in phase 3 clinical trials; on 5-year follow-up, 15–30% of ipilimumab treated patients were still alive, suggesting striking response durability [136]. Combination ipilimumab and fotemustine demonstrated 50% disease control for patients with brain metastases in a phase 2 trial, with a 12.7 month median survival and a 3-year survival rate of 27.8% [144]. In another study of patients with previously untreated metastatic melanoma, ipilimumab combined with dacarbazine extended survival beyond dacarbazine alone (median survival of 11.2 vs. 9.1 months, respectively) [142]. At 3 years, 20.8% of patients receiving combination ipilimumab/dacarbazine remained alive, compared to 12.2% for the dacarbazine arm. The almost 10% difference between survival curves for over 36 months corroborates the ability of ipilimumab to drive long-term response rates in a small proportion of patients.

A phase 2 multi-institutional trial evaluating the efficacy of high-dose ipilimumab (10 mg/kg 4x weekly)

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**Figure 3: Immunologic recognition and elimination of tumors.** Tumor antigen is presented by an antigen presenting cell (APC) on the major histocompatibility complex (MHC), which serves as the ligand for the T-cell receptor (TCR). A second costimulatory signal (CD80/86) binding to CD28 on the lymphocyte is necessary for T-cell effector phase activation.
in intracranial melanoma demonstrated disease control in 24% of patients after three months, with 11% partial response, a portion of which were durable [145]. Of particular significance, these data suggest that ipilimumab in patients with CNS disease provides a similar measure of disease control as in those without CNS metastases; active intracranial disease had previously been excluded for all clinical trials with ipilimumab monotherapy. These findings indicate that ipilimumab may mitigate the poor prognosis of CNS disease, highlighting the systematic efficacy of immunotherapy.

Importantly, concomitant steroid use may also have an effect on patient response. Although steroids may be thought to improve certain symptoms, they also exert an immunosuppressive effect. In the referenced phase 2 ipilimumab trial [145], patients not requiring corticosteroids for clinical or radiological control displayed the most favorable outcomes (24% versus 10% response rate), suggesting that steroid use may negatively influence ipilimumab efficacy. Of note, however, the cohort requiring corticosteroids displayed more severe symptoms, which could partially account for the decrease in response rate.

Follow-up for 177 advanced melanoma patients enrolled in the earliest ipilimumab trials demonstrated median response duration of up to 7 years [143]. Notably, a proportion of initially reported partial responses progressed into complete responses after a prolonged

Figure 4: (A) Immune targets and (B) current immunotherapies under investigation for metastatic melanoma. APC, antigen presenting cell; CTLA-4, cytotoxic T-lymphocyte associated protein 4; MHC, major histocompatibility complex; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; TCR, T-cell receptor; T-reg, regulatory T-cell
period of time, with average complete response attained at 30 months after treatment initiation. This extensive temporal interval before achieving complete tumor response likely reflects the time necessary for T-cells to uncouple from CTLA-4 mediated inhibition, undergo activation, and subsequently infiltrate and eradicate the tumor. In support, melanoma biopsy after ipilimumab treatment shows clear evidence of tumor infiltrating lymphocytes (TIL) [146, 147].

Side effects of ipilimumab therapy include immune-mediated diarrhea, rash, adrenal insufficiency, and hypophysitis [148]. In a phase 3 trial of 676 patients, 14 deaths (2%) were drug-related, half of which were associated with immune-related adverse events [136]. The mechanistic role of CTLA-4 during early stages of T-cell activation—which leads to a more diffuse and nonspecific activation pattern compared to effector phase regulation—may explain the gamut of immune-triggered adverse events observed in clinical studies.

PD-1 checkpoint inhibition

In comparison to the role of CTLA-4 early in T-cell activation, PD-1 and its ligands (PD-L1 and PD-L2) regulate the effector phase of T-cell activation (Figure 4A). PD-1 couples to ligand outside the lymph node in the peripheral tissues (e.g., the tumor cell microenvironment), leading to downregulation of effector function resulting in an “exhausted” phenotype and lymphocyte apoptosis [149]. PD-1 and PD-L1 expression colocalizes with TIL and circulating interferon-gamma in metastatic melanoma, suggesting a role in countering the host immune response [150]. Inhibition of the PD-1/PD-L1 axis in vitro reinstates T-cell eradication of melanoma cells [151]. PD-L1 expression is observed in approximately 47% of intracranial melanoma metastases [152].

Two PD-1 inhibitors have been approved by the FDA for the first-line treatment of metastatic melanoma (in September 2014 and January 2015, respectively): nivolumab (Opdivo®; Bristol-Myers Squibb, New York City, New York, USA) and pembrolizumab (formerly MK-3475 or lambrolizumab; Keytruda®; Merck, Kenilworth, New Jersey, USA). Nivolumab confers significant improvement to overall survival when compared with dacarbazine in previously untreated non-\textit{BRAF}-mutant melanoma patients [153]. As with CTLA-4 inhibition, the duration of response to nivolumab appears to be relatively long-lived when compared to other therapeutic modalities. A phase 1 trial showed a mean overall response rate of 28% in patients with advanced, previously treated melanoma, with 62% experiencing a response durability of a year or longer [154]. During subsequent follow-up, the median OS was 16.8 months across all dosing regimens (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg), with a peak of 20.3 months at the 3 mg/kg dose [155]. By targeting effector phase lymphocytes, PD-1 inhibition exhibits a more restricted pattern of immune upregulation compared with CTLA-4 suppression, which grants fewer immune-mediated side effects and a shorter time lag before complete tumor response than with ipilimumab, as TILs are already present in metastases.

Pembrolizumab also appears promising in metastatic melanoma, with measurable response rates observed in 37–38% of patients, tumor size reduction in 77%, and a median response durability of > 11 months at time of report [156]. In a 2016 trial, significant interim responses to anti-PD1 therapy in 39 patients with brain metastases were observed, with additional studies on intracranial melanomas presently underway [157].

Interestingly—and contrasting with molecular therapy—previous treatment with ipilimumab does not significantly affect the likelihood of mounting a sizeable tumor response with anti-PD1 therapy [156]. Additionally, severity of adverse events experienced with ipilimumab are not predictive of adverse events during second-line PD1 inhibition [158].

Studies evaluating PD-1 blocking antibodies specifically in patients with intracranial melanoma metastases are underway (NCT02374242, NCT02320058). Other anti-PD-1 antibodies in development include CT011 and PDR001 [159]. Expression of PD-1 ligand (PD-L1) by tumor lines is being investigated as a predictive biomarker with distinct genetic and morphological characteristics (e.g., increased aggressiveness) [160], with preliminary data suggesting that tumors lacking PD-L1 expression are less likely to respond to PD-1 inhibition compared to tumors expressing PD-L1 [161]. Several PD-L1 antibodies, including BMS-936559 and MPDL-3280A, are also under clinical testing. Initial evidence demonstrates that PD-L1 suppression induces durable melanoma regression, with an objective response rate of 17% at 6 months [162].

Combinatorial immunotherapy

CTLA-4 and PD-1 co-inhibition offers an additional domain of clinical investigation. In an early clinical trial of combination nivolumab and ipilimumab in advanced melanoma patients, 53% of treatment-naïve patients had an objective response with rapid and extensive (80%) regression of tumor, although a number of adverse side effects—including hepatic, gastrointestinal, and renal events—were reported [163]. A more recent phase 1 study confirmed a response rate of 61% for ipilimumab/nivolumab combination therapy versus 11% for ipilimumab monotherapy, with complete response reported in 22% and 0%, respectively [164]. Accelerated approval of the combination for \textit{BRAF}-mutant melanoma was granted by the FDA in January 2016. A phase 2 study investigating combination ipilimumab and nivolumab in active intracranial metastases is currently underway (NCT02320058).
Of note, the CTLA-4 and PD-1 immunological pathways are complementary and nonredundant, with CTLA-4 inhibition affecting early T-cell activation in lymph nodes and PD-1 suppression affecting effector T cells in peripheral tissue. Interestingly, in an animal model of melanoma, CTLA-4 inhibition resulted in a higher proportion of TIL expressing PD-1 while PD-1 inhibition led to increased TIL expression of CTLA-4 [165]. Treatment with CTLA-4 or PD-1 monotherapy may trigger upregulation of compensatory checkpoint mechanisms, highlighting the therapeutic potential of targeting multiple immunological pathways.

Other immunotherapeutic treatments

Checkpoint inhibition is a recent evolution of long-standing experience with immunotherapy in melanoma patients. Interleukin-2 (IL-2) has been FDA-approved since 1998 for advanced melanoma therapy, based on data from phase 2 studies [166, 167]. High-dose administration is associated with overall response rates of 16%, with penetration to all sites of disease, including the CNS. Median response durability is greater than six months; in 5% of patients with metastatic spread, clinical benefit may be observed for decades [168]. At high concentrations, however, IL-2 is significantly toxic, causing capillary leak syndrome and increased cerebral edema, thereby restricting its therapeutic profile to patients without cardiopulmonary morbidities and with good performance status.

Adoptive cell transfer (ACT), another immunotherapy strategy, involves collection of lymphocytes, either TILs or blood T cells, from the patient, followed by \textit{ex vivo} activation and expansion (e.g., through the use of chimeric antigen receptors (CAR), which are used to graft disease-targeted monoclonal antibodies onto T cells), and subsequent infusion of processed cells back into the patient to induce an immune response [169]. In a recent report of ACT in metastatic melanoma patients, an overall response rate of 56% was observed in 93 patients [170]. No relapses were reported within a follow-up of 31 months among the 11% who achieved a complete response.

In addition, inhibition of auxiliary coinhibitory molecules—such as lymphocyte activation gene 3 (LAG-3), indoleamine-2,3-dioxygenase (IDO), arginine deaminase, prostaglandin E2, VEGF, T-cell immunoglobulin domain and mucin domain 3 (TIM-3), IL-6, IL-10, and other cytokines—are currently in clinical trials (Figure 5). Preliminary clinical results have also suggested the plausibility of novel immunotherapeutic combinations, including ipilimumab and high-dose IL-2 [143]. Other potential complementary therapies include vaccines and regulatory T-cell suppression. For intracranial melanoma metastases, combination of immunotherapeutic treatment with adjuvant SRS synergistically improves BBB permeability, stimulates cytokine release, and increases antigen presentation on melanoma surface cells, with durability rates of > 4 years [171–173].

Resistance mechanisms of immune escape

Resistance via immune escape has been reported for various immunotherapeutic treatments, although less frequently than with BRAF inhibition. Potential mechanisms include selection of antigen-deficient tumor variants, induction of T-cell tolerance, antigen loss, and inflammation-induced reversible loss of melanocytic antigens [63, 174]. Melanoma-associated antigens include tumor-associated testis-specific antigens (e.g., MAGE, BAGE, and GAGE), melanocyte differentiation antigens (e.g., Melan-A/MART-1, tyrosinase), and aberrantly expressed or mutated molecules (e.g., CDK4, beta-catenin) [175].

Figure 5: Immunotherapy options beyond checkpoint inhibition.
In conditions of increased lymphocytic cytotoxicity against melanoma antigens, a portion of tumor cells switch from a differentiated to a dedifferentiated phenotype in response to T-cell driven inflammation [176, 177]. This process is mediated by tumor necrosis factor alpha (TNFα), which camouflages tumor cells against the immune system and is reversible upon discontinuation of therapy and resolution of inflammation. Upregulation of immunosuppressive mechanisms in melanoma may also inhibit T-cell activation, including IDO, PD-L1/B7-H1, and FoxP3+ regulatory T cells [178]. These factors serve as negative feedback mechanisms following T-cell infiltration, suggesting suppressive regulatory immune checkpoints as viable future clinical targets.

In vitro experiments have also demonstrated a role for apoptosis regulation as a means of modulating tumor resistance, through downregulation of death receptors (DRs) and the TNF-related apoptosis-inducing ligand (TRAIL) cytotoxic pathway [179]. Resistant melanoma cell lines demonstrate DR5 downregulation and an inverted proportion of pro- versus anti-apoptotic molecules, the effects of which can be countered by histone deacetylase (HDAC) inhibitors. This category of compounds prevents silencing of pro-apoptotic genes by blocking HDAC from deacetylating histone moieties. One such drug, vorinostat, has received FDA approval for the treatment of cutaneous T-cell lymphoma. Delivery of chromatin remodeling drugs to immune-resistant melanomas may be able to counter acquired resistance by shifting the intracellular climate towards a pro-apoptotic status through increased DR expression. Indomethacin, a non-steroidal anti-inflammatory drug, has also been shown to enhance TRAIL-mediated apoptosis through upregulation of DR5 and down-modulation of survivin in human melanoma cell lines [180].

Additional modalities of acquired resistance include mechanisms that interfere with T-lymphocyte activity within the melanoma microenvironment [181]. Multiple checkpoint molecules have been observed to dampen the immune response, including LAG-3, TIM-3, and B- and T-lymphocyte attenuator (BTLA) [182]. Immunotherapy may also confer a fitness advantage to melanoma subpopulations with loss of MHC expression, which renders the tumor effectively invisible to the adaptive immune system [63, 183].

Unlike with BRAF and MEK inhibitors, treatment failure with one immunotherapy does not preclude response to others; patients resistant to ipilimumab can still have a response to anti-PD-1, and vice versa [156, 184]. Interestingly, retreatment is possible in tumor recurrences [185, 186], suggesting the activation and expansion of a new cohort of T-cells specific to the evolving tumor antigen repertoire.

Current knowledge regarding clinical benefits of immunotherapy may provide guidance for future trials of novel agents with respect to metastatic melanoma. Drugs with low response rates sustained by intratumoral lymphocyte infiltration—e.g., anti-CTLA4 antibodies—should focus on response durability as the main trial endpoint [187]; agents with high response rates and well-characterized mechanisms should focus on clinically meaningful duration. Combination immunotherapies, in turn, should focus on increased durability of response rates after addition of the co-therapeutic agent. Pharmacokinetic aspects relative to tumor penetrance, drug concentration in tumor cells, molecular stability, and receptor occupancy should also be noted. Improved characterization of drugs under development may accelerate and streamline trial design and meaningful interpretation of clinical endpoints.

**CONCLUSIONS**

Since 2011, seven novel agents have been introduced for targeted treatment of late-stage melanoma, including patients with intracranial disease—vemurafenib, dabrafenib, trametinib, cobimetinib, ipilimumab, nivolumab, and pembrolizumab. Therapeutic choices should be personalized based on multiple factors: BRAF mutational status, comorbidities, tumor burden, and immune status.

Current consensus in the literature indicates that patients with BRAF mutant brain tumors should receive a BRAF inhibitor or combinatorial therapy with BRAF and MEK co-inhibition. There is no definitive clinical evidence suggesting that one inhibitor outperforms the other, although consideration should be taken regarding side effects. The rising epidemic of BRAF inhibitor resistance, as a consequence, invokes increasing combinatorial strategies for treatment of BRAF-mutant metastatic melanoma. Immunotherapy offers additional treatment options in exploiting the endogenous immune system to destroy metastatic tumor, with strikingly durable responses of several years in some. In addition, conventional treatments such as surgery and radiation continue to play a role in control of tumor progression for select clinical indications.

Despite the new ammunition against metastatic melanoma over the past five years, prognosis remains guarded. Further investigations into countering resistance, minimizing toxicity, optimizing combination therapies, and improving survival remain critically needed. By formulating a better framework for understanding the efficacy and limitations of current therapeutic modalities, improved prognoses and disease management may be attainable for intracranial melanoma diagnoses.

**CONFLICTS OF INTEREST**

None.

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