Principles of Targeted Therapy for Melanoma

James Sun, MD, Michael J. Carr, MD, Nikhil I. Khushalani, MD*

KEYWORDS

• BRAF • MEK • NRAS • KIT • Brain metastasis • Melanoma • Mutation

KEY POINTS

- The mitogen-activated protein kinase (MAPK) pathway is involved in the pathogenesis of most cutaneous melanomas.
- Up to 50% of melanomas arising in sun-damaged skin harbor a single nucleotide substitution at codon 600 in the *BRAF* oncogene (*BRAF V600*).
- *BRAF V600* mutations provide a therapeutic target with BRAF/MEK inhibitors, which provide rapid clinical results in most patients, but are also associated with high rates of treatment resistance through MAPK reactivation.
- The role of perioperative use of BRAF-targeted therapy is evolving.
- Activating *KIT* mutations are rarely found in melanomas but may be an actionable target of therapy, which is the subject of several ongoing clinical trials.

INTRODUCTION

Over the past decade, there has been significant advancement in the understanding of the pathophysiology of melanoma. These advancements have led to the systematic development of new effective therapies for advanced disease in the form of molecularly targeted therapy and immunotherapy. Randomized trials have also demonstrated efficacy in reducing relapse after complete surgical resection of stage III or stage IV melanoma, thus making modern management of melanoma a multidisciplinary endeavor. The most common activating mutations in melanoma cells are *BRAF*, *NRAS*, and *KIT* mutations.[1] These mutations cause derangements in cell signaling pathways, leading to unchecked tumor proliferation. The cell signaling pathways implicated in the progression of benign melanocytes to malignant disease are now better understood. These pathways may be the key to identifying new therapeutic targets and providing more options against this devastating disease.

Department of Cutaneous Oncology, Moffitt Cancer Center, 10920 North McKinley Drive, 4th Floor, Tampa, FL 33612, USA
* Corresponding author.
E-mail address: nikhil.khushalani@moffitt.org

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BRAF MUTATIONS

The mitogen-activated protein kinase (MAPK) pathway is a signaling pathway that is normally responsible for intracellular processes, which include acute hormone responses, embryogenesis, cellular differentiation, cellular proliferation, and apoptosis. This pathway is activated by extracellular binding of receptor tyrosine kinases (RTK), leading to activation of the rat sarcoma (RAS) family protein, which subsequently activates intracellular serine-threonine protein kinases of the rapidly accelerated fibrosarcoma (RAF) family (ARAF, BRAF, CRAF). Activation of RAF leads to the phosphorylation of MAPK extracellular receptor kinase (MEK), which in turn phosphorylates extracellular signal-regulated kinase (ERK). ERK activation promotes cellular proliferation and activates mitochondrial proteins, which promote growth and inhibit apoptosis.[2,3] Activated ERK also provides negative feedback at various levels of the pathway.

The MAPK pathway has an important role in melanoma oncogenesis. Derangements in the MAPK pathway are most commonly caused by single nucleotide substitutions at codon 600 in the *BRAF* oncogene, which encodes the BRAF protein. This mutation is found in approximately 50% of all melanomas. *BRAF* mutations are more frequent in melanomas that develop in sun-exposed skin.[4] This mutation leads to unregulated activation of RAS independent of RTK binding, thus causing constitutive activation of MEK and ERK, resulting in unchecking cellular proliferation.[3] The most common mutation at this locus is due to a single nucleotide valine-to-glutamic acid substitution (*BRAFV600E*), which occurs in approximately 90% of *BRAF*-mutant melanomas. The second most common mutation is *BRAFV600K* (substituting lysine for valine), which accounts for another 5% to 6% of *BRAF*-mutant melanomas. Other observed, albeit less common mutations include *BRAFV600D* and *BRAFV600R*. BRAF mutations are associated with approximately 80% of melanocytic nevi, suggesting an early role oncogenesis. However, only a small portion of nevi actually progress to melanoma.[5–7]

NEUROBLASTOMA RAT SARCOMA MUTATIONS

Activating mutations within the RAS family are seen in approximately 20% of all melanomas at diagnosis and are most common in the human neuroblastoma RAS (NRAS) GTPase. *NRAS* mutations are mutually exclusive with *BRAF* mutations. The most common *RAS* mutations occur at codons 12, 61, or 13; 15% of cases have point mutations. All of these are activating mutations that exert a different effect on the NRAS protein. However, the end result is the same, leading to GTP-bound, activated RAS protein.[8] NRAS amplification and mutation cause constitutive activation of the MAPK pathway as well as the phosphatidylinositol 3-kinase (PI3K) pathway.[5–7]

PHOSPHATIDYLINOSITOL 3-KINASE PATHWAY

Stimulation of the PI3K pathway has been found to occur in 30% to 60% of melanomas through functional loss of the tumor suppression protein PTEN, which is associated with *BRAF V600E* mutations.[9] Also implicated in this line is the activation or amplification of serine/threonine protein kinase AKT3 in 40% to 60% of melanomas.[10–12] This pathway follows the RTK-RAS-PI3K-(PTEN)-AKT3 signal cascade to the mitochondrial antiapoptotic protein BCL2 and cellular growth regulator mTOR (mammalian target of rapamycin). Upstream of RAS, amplifications or activating mutations in the gene encoding the RTK for stem cell factor, KIT, can also activate this pathway.[2,6,12] This pathway has also been implicated in the development of melanoma brain metastases (MBM).[13]

CURRENT REGIMENS FOR *BRAF*-MUTATED ADVANCED MELANOMA

Understanding of the MAPK pathway has led to identification of therapeutic targets with development of highly specific BRAF and MEK inhibitors. BRAF inhibitors selectively target the mutated BRAF kinase, thus decreasing signal transduction through the MAPK pathway. Vemurafenib was the first approved BRAF inhibitor in 2011 on the basis of the BRIM-3 (*BR*AF *I*nhibition in *M*elanoma-3) trial.[14] This phase 3 trial conducted in 675 patients with previously untreated advanced or unresectable BRAF *V600* mutant melanoma demonstrated superior response with vemurafenib versus dacarbazine for the treatment of *BRAF*-mutant melanoma, with an overall response rate (ORR) of 48% versus 5% with dacarbazine. In the final report of this trial conducted at a median follow-up period of 13.4 months for patients on the vemurafenib arm and 9.2 months for those on the dacarbazine arm, overall survival (OS) was significantly superior for vemurafenib.[15] The median OS was 13.6 months for vemurafenib-treated patients versus 9.7 months on the dacarbazine arm (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.67–0.98, $P = .03$). The landmark analyses on vemurafenib demonstrated OS at 3 and 4 years to be 21% and 17%, respectively. It should be noted that 84 of 338 patients on dacarbazine crossed over to vemurafenib during the conduction of this study. The OS remained significant in favor of vemurafenib regardless of censoring results at crossover. In a previous report on this trial, the median progression-free survival (PFS) also significantly favored the vemurafenib arm (6.9 months vs 1.6 months, HR 0.38, 95% CI 0.32–0.46, $P<.0001$).[16] Efficacy results for other approved BRAF inhibitors, including dabrafenib and encorafenib, are very similar.[17]

Although BRAF-inhibition produces dramatic tumor response in most patients, these responses are limited by rapid development of treatment resistance at a median time of 5 to 7 months.[18] The addition of an MEK inhibitor, a downstream component of the MAPK pathway, delays the onset of resistance. Combination BRAF/MEK inhibition has also demonstrated improved treatment response, PFS, and OS compared with BRAF-inhibitor monotherapy. The current standard of care is thus to use combination targeted therapy rather than single-agent BRAF or MEK inhibitor therapy for eligible patients whose tumor harbors a mutation in *BRAF V600*. The 3 approved combination therapies are dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib on the basis of several large phase 3 trials affirming superiority of the combination.[19–22]

The evolution from single-agent BRAF inhibitor therapy to combination BRAF plus MEK inhibitor therapy was rapid and with remarkably consistent results, at least for the comparator arm in this trial. In the COMBI-d study, 423 untreated patients with unresectable stage IIIC or metastatic melanoma harboring a mutation in BRAF *V600E/K* were randomized to receive combination dabrafenib (150 mg orally twice daily) plus trametinib (2 mg orally daily) versus dabrafenib alone at the same dose and schedule. Several updates with mature follow-up to the results of this trial have been published since the original report in 2014.[19,23,24] The confirmed response rate per Response Evaluation Criteria in Solid Tumors (RECIST) was 68% for the combination and 55% for dabrafenib alone, with corresponding complete response rates of 18% and 15%, respectively, for the 2 groups. The median PFS was 11.0 months versus 8.8 months, respectively (HR 0.67, 95% CI, 0.53–0.84, $P = .004$). At the time of an updated data cutoff in February 2016, the 3-year PFS and OS for dabrafenib plus trametinib were 22% and 44%, respectively, with corresponding values for the monotherapy dabrafenib arm of 12% and 32%, respectively. With this median follow-up time of $\geq$36 months for patients who were alive, 19% remained on therapy

with the combination versus 3% on the monotherapy arm, without any new signals of toxicity concern, suggesting that chronic administration of these agents was safe. In a larger phase 3 trial (COMBI-v), the same doublet of dabrafenib and trametinib was compared with vemurafenib alone with remarkably similar results of efficacy.[20] The response rates were 64% versus 51%, with median PFS of 11.4 months versus 7.3 months (HR 0.56, 95% CI, 0.46–0.69, $P<.001$), all favoring the combination arm. Similarly, the 1-year OS was 72% for the combination versus 65% for vemurafenib alone (HR 0.69, 95% CI, 0.53–0.89, $P = .005$).

Given the finite time to progression that is commonly observed with targeted therapy, a pooled analysis examining the long-term efficacy of dabrafenib plus trametinib within the COMBI-d and COMBI-v trials was recently published.[25] This study reported data on 563 patients treated with this combination. The median PFS and OS were 11.1 months and 25.9 months, respectively. The PFS at 4 years was 21% and 19% at 5 years. The corresponding landmark analyses for OS were 37% and 34%, respectively. This excellent efficacy in one-third of patients treated initially with targeted therapy appears to contradict the prior notion that durable responses can only be seen with immunotherapy. Factors associated with a favorable prognosis and improved PFS and OS included older age, female sex, *BRAF V600E* status, normal lactate dehydrogenase, and fewer than 3 sites of visceral metastatic disease. In those patients who achieved a complete objective response to therapy (19%), the 5-year OS was an impressive 71%. An important consideration in this analysis was the fact that 88% (51/59) patients who were progression free at 5 years continued on the original therapy, either dabrafenib, trametinib, or both drugs. Conversely, in the limited available data on progression (n = 15) in responding patients who had discontinued therapy before progression, the median time to progression was only 3.7 months. Thus, the question of elective discontinuation of therapy based on depth of response remains unclear. Patients on targeted therapy should continue treatment as long as tolerable in the face of ongoing benefit of response.

The combination of vemurafenib with the MEK inhibitor cobimetinib gained regulatory approval in the United States for advanced melanoma based on the coBRIM trial, a randomized comparison of this combination to vemurafenib plus placebo in *BRAF V600*-mutant melanoma.[21,26] The primary endpoint of PFS was superior in the combination (12.3 months) versus the monotherapy arm (7.2 months) (HR 0.58, 95% CI 0.46–0.72, $P<.001$). Similarly, median OS was also longer at 22.3 months versus 17.4 months (HR 0.70, 95% CI, 0.55–0.90). The COLUMBUS trial similarly confirmed the superiority of yet another combination inhibiting the MAPK pathway compared with BRAF inhibition alone. In this 3-arm study, encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) was compared with encorafenib alone or vemurafenib alone.[27] The combination improved median PFS to 14.9 months versus 7.3 months for vemurafenib alone (HR 0.54, 95% CI, 0.41–0.71, $P<.001$). Similarly, median OS in patients treated with encorafenib and binimetinib was 33.6 months compared with 16.9 months in those who received vemurafenib (HR 0.61, 95% CI, 0.47–0.79, $P<.001$). The combination was also superior to encorafenib alone for both these comparisons.

Although the PFS and OS using encorafenib and binimetinib are numerically higher than that achieved with the other 2 combinations, it should be noted that these regimens have not been compared directly with one another, nor is that likely to occur. However, the consistency of results across the single-agent arms in these trials is remarkable. Thus, decisions on choosing a specific combination are typically made based on the predicted toxicity profile and physician-patient preference. The current National Comprehensive Cancer Network (NCCN) guidelines

recommend BRAF/MEK inhibitor combination therapy with 1 of the 3 approved first-line regimens for the treatment of unresectable or distant metastatic disease in *BRAF V600* mutated melanoma.[28] There are currently no data available to guide selection of targeted therapy versus immune checkpoint inhibition as the initial therapy for unresectable or metastatic *BRAF V600* mutant melanoma; however, the NCCN guidelines suggest factoring in the rate of disease progression. Targeted therapy tends to elicit a rapid clinical response and may be more appropriate initial therapy in the setting of symptomatic disease. Vemurafenib and dabrafenib are also approved for monotherapy and only recommended in situations whereby combination therapy is contraindicated or not tolerated, and immune checkpoint inhibitor therapy is not a preferred option (eg, active autoimmune disease, organ transplant recipient, ongoing immunosuppressive therapy). There is also little definitive clinical trial data to guide selection of second-line treatment; however, all 3 combination BRAF/MEK inhibitor combinations remain reasonable options after failure of front-line immunotherapy (category 2A recommendation by NCCN).

ADJUVANT AND NEOADJUVANT THERAPY OF *BRAF*-MUTANT MELANOMA

Until recently, adjuvant systemic therapy for surgically resected cutaneous melanoma was limited to interferon or ipilimumab, both agents with substantial toxicity. The risk of relapse is predominantly linked to the depth and ulceration of the primary tumor as well as the presence of in-transit and/or nodal metastases. Before the results of the second Multicenter Selective Lymphadenectomy Trial -II, patients with positive sentinel nodes routinely underwent completion nodal dissection (CLND).[29] The lack of improvement of melanoma-specific survival with immediate CLND has markedly reduced the number of patients with sentinel node metastasis undergoing this procedure. This paradigm change in the surgical management of melanoma is important to recognize in the context of delivery of postoperative systemic therapy because all published trials of adjuvant treatment in melanoma mandated a CLND before treatment. The assumption of similar benefit of adjuvant therapy for sentinel node metastasis without CLND is thus presumed in the modern era of immunotherapy and targeted therapy.

The COMBI-AD trial was a double-blind, placebo-controlled randomized phase 3 trial aimed to assess the relapse-free survival (RFS) of combination dabrafenib and trametinib versus matched placebo administered for 12 months in resected stage III (per American Joint Committee on Cancer [AJCC], 7th edition) cutaneous melanoma harboring *BRAF V600E/K* mutations.[30,31] Patients with stage IIIA disease were required to have lymph node metastasis greater than 1 mm. Among 870 randomized patients, most (81%) had stage IIIB or IIIC disease. At mature follow-up exceeding 40 months, the median RFS had not been reached for the dabrafenib plus trametinib arm compared with 16.9 months in the placebo arm (HR 0.49, 95% CI, 0.40–0.59). The corresponding 4-year RFS rates were 54% and 38%, respectively. In the initial report at the first interim analysis for OS, the 3-year estimate for OS was 83% for the combination therapy versus 77% for placebo (HR 0.57, 95% CI, 0.42–0.79, $P = .0006$). This difference however did not cross the prespecified conservative interim boundary of statistical significance at $P = .00019$. In the follow-up report, the number of events needed for the subsequent prespecified OS interim analysis had not been reached. Using a Weibull cure-rate model, the estimated cure rate (lack of relapse) was 54% for the treatment arm versus 37% for the placebo arm. In addition, a post hoc analysis for RFS across disease stage

defined by AJCC, 8th edition indicated benefit across all subgroups (stages IIIA–D) for combination therapy. This combination of dabrafenib and trametinib was approved by the Food and Drug Administration for the adjuvant therapy of completely resected stage III melanoma in 2018. Combination BRAF/MEK inhibition has not been directly compared with approved anti-PD1 agents (nivolumab or pembrolizumab)[32,33] as adjuvant therapy, and any one of these options are reasonable choices following complete resection of node-positive *BRAF V600* mutant cutaneous melanoma.

With the availability of effective systemic therapy in melanoma, there has been growing interest in neoadjuvant therapy for macroscopic nodal metastatic melanoma or disease that is considered unresectable at clinical presentation. This approach has several theoretic advantages, including control of micrometastatic disease, improved regional control, "debulking" an unresectable or borderline resectable tumor mass toward making surgery feasible, and possibly sparing a patient from unnecessary surgery in the face of progressive disease on upfront systemic therapy. In addition, this approach is suited for systematic tissue study to identify biomarkers of response and resistance as well as understanding pathologic response at the time of surgery. Given the high response rates to MAPK-targeted therapy, these agents are ideal choices for investigation in the neoadjuvant setting, although prospective data to date have been scant. In a single-institution randomized phase 2 trial, patients with surgically resectable and locally advanced clinical stage III (at least 1 palpable node with short axis >1.5 cm, or an in-transit metastasis >1 cm) or oligometastatic stage IV melanoma were randomized 1:2 to surgery upfront followed by adjuvant therapy or 8 weeks of neoadjuvant dabrafenib plus trametinib followed by surgery and 44 additional weeks of the same combination therapy.[34] This trial was halted early when clear superiority for the investigational approach was identified. The radiographic response to neoadjuvant therapy was 85%, and 7/12 (58%) patients who underwent surgery had a pathologic complete response (pCR). The median event-free survival was 19.7 months in the neoadjuvant arm compared with only 2.9 months in the standard of care arm (HR 0.016, 95% CI 0.00012–0.14, $P<.001$). Of note, only 1 patient in the latter cohort opted for adjuvant biochemotherapy, whereas the other 6 patients were observed expectantly. In an Australian prospective cohort (NeoCombi), 35 patients with stage IIIB/C melanoma were treated with 12 weeks of neoadjuvant dabrafenib and trametinib followed by surgery and an additional 40 weeks of the same systemic treatment.[35] The RECIST response was 86%, and the pCR rate was 49%. There was no progression noted during neoadjuvant therapy, and the median RFS was 23.3 months. Surgical complications occurred in 22 patients, most commonly seroma and postoperative infections requiring intravenous antibiotics. In a retrospective report from the authors' experience at Moffitt Cancer Center, 23 *BRAF V600* mutant melanoma patients with stage IIIC/IV disease were treated with neoadjuvant MAPK-targeted therapy (BRAF inhibitor monotherapy or in combination with an MEK inhibitor) for a median of 6.6 months before surgery.[36] With mature median follow-up of 43 months (range, 10–95), the radiographic response rate was 87%, and pCR was achieved in 10 patients (44%). Among the latter group, only 1 patient experienced relapse of disease, whereas 8/13 (62%) patients with residual tumor in the surgical resection specimen had relapsed. The influence of pathologic response to neoadjuvant therapy on subsequent systemic therapy has yet to be studied. The International Neoadjuvant Melanoma Consortium has made recent recommendations in an attempt to standardize study protocols in this arena for optimization of clinical care and research priorities.[37]

TARGETED THERAPY FOR MELANOMA BRAIN METASTASES

Brain metastases from melanoma are a known devastating complication with poor outcomes.[38] The treatment of MBM has historically been based on local treatment with surgery, whole-brain radiation, and stereotactic radiosurgery. Recent advances in systemic therapy have improved the median OS to 14 to 23 months.[38–40] Chemokine receptor type 4 (CCR4) is a transmembrane receptor that is overexpressed in melanoma cells that metastasize to the brain and is predictive of MBM in murine models.[13,41] CCR4 activation leads to activation of the PI3K pathway. Melanoma cells attempt to overcome the blood-brain barrier using 2 mechanisms. They secrete serine proteases, to break down occludin and claudin-5 (transmembrane proteins), and cytoplasmic plaque protein ZO-1, to disrupt the endothelial tight junction.[42] Melanoma cells then release matrix metalloproteinase-2 (MMP-2) and heparanase, which are extracellular matrix degrading enzymes, to disrupt the basement membrane.[43] At this point, melanoma cells are free to invade the brain parenchyma. The janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway has been implicated in neoangiogenesis of brain metastases.[44,45] The PI3K pathway promotes MBM via upregulation of CCR4, heparanase, as well as vascular endothelial growth factor and STAT3. The MAPK pathway has also been implicated in the development of MBM. In a study of 1048 patients by Adler and colleagues,[46] the presence of *BRAF* and *NRAS* mutations was associated with increased odds of developing metastases in the central nervous system. There is evidence that downregulation of the MAPK pathway after treatment with BRAF/MEK inhibition may lead to upregulation of the PI3K pathway, leading to resistance.[47,48] As a result, melanomas that develop treatment resistance may be predisposed to metastasize to the brain.[49,50]

The BREAK-MB study evaluated activity and safety of dabrafenib monotherapy in *BRAF V600E*- and *V600K*-mutant melanomas with brain metastases.[51] Treated were 172 patients: 89 patients had not received previous local treatment (cohort A) and 83 patients had progressed after prior local treatment (cohort B). In patients with *BRAF V600E* mutations, the intracranial response rate was 39% (29/74 patients) in cohort A versus 31% (20/65 patients) in cohort B. ORR was 38% and 31% in cohorts A and B, respectively. The median PFS was approximately 4 months, and OS was approximately 8 months. Patients with *BRAF V600K* mutations (n = 33) had worse ORR; 7% (1/15) in cohort A versus 22% (4/18) in cohort B. Similarly, vemurafenib has demonstrated intracranial efficacy in a phase 2 study by McArthur and colleagues.[52] Among 146 patients enrolled, 90 were therapy naïve for MBM (cohort 1), whereas 56 patients had received prior treatment (cohort 2). The intracranial response rate was 18% in both cohorts by independent review, which was lower than extracranial response (33% and 23%, respectively). The median intracranial PFS was 3.7 months and 4 months in cohorts 1 and 2, respectively; median OS was 8.9 months and 9.6 months, respectively.

The phase 2 COMBI-MB study assessed the activity and safety of combination dabrafenib and trametinib therapy in MBM patients with *BRAF V600* mutations.[49] They established 4 patient cohorts: cohort A (n = 76), *BRAF V600E*-mutant, asymptomatic MBM without prior local brain-directed therapy and Eastern Cooperative Oncology Group (ECOG) performance status of $\leq$1; cohort B (n = 16), *BRAF V600E*-mutant, asymptomatic MBM with prior local therapy and ECOG performance status of $\leq$1; cohort C (n = 16), *BRAF V600D/E/K/R*-mutant, asymptomatic MBM with or without prior local therapy and ECOG performance status of $\leq$1; cohort D (n = 17), *BRAF V600D/E/K/R*-mutant, symptomatic MBM with or without prior local therapy and ECOG performance status of $\leq$2. Intracranial response rates were 58%,

56%, 44%, and 59% in cohorts A through D, respectively. In cohort A, extracranial response rate was 55% with median PFS of 5.6 months and median OS of 10.8 months; median duration of intracranial response was 6.5 months, and median duration of extracranial response was 10.2 months. This study demonstrated improved activity of dabrafenib + trametinib in MBM in comparison to dabrafenib monotherapy and vemurafenib.[51,52] Response rates were better than traditional local brain-directed therapies; however, the duration of disease control is shorter than in melanoma patients without brain metastases. The safety profile of dabrafenib plus trametinib was similar as previously reported studies with manageable adverse events in patients with MBM.

In an era of expanding systemic options for MBM, a multidisciplinary evaluation is essential in order to optimize outcomes using all available modalities of therapy. Studies combining targeted therapy with immunotherapy in this setting have been planned.

NRAS MUTATIONS IN MELANOMA

As discussed previously, *NRAS* mutations resulting in constitutive activation of the MAPK pathway are seen in about one-fifth of all melanomas. Given the inherent difficulty in targeting *NRAS* directly and recognition of the downstream effects of *RAS* activation, MEK inhibition has been explored as an option to inhibit the MAPK pathway in *NRAS* mutant melanoma. Binimetinib, an inhibitor of MEK 1/2, demonstrated a modest 20% response rate in *NRAS* mutant melanoma, all partial responses.[53] In a phase 3 trial of *NRAS*-mutant stage IIIC or stage IV melanoma, either untreated or with progression on immunotherapy, 402 patients were randomized 2:1 to receive binimetinib 45 mg orally twice daily or standard dacarbazine administered intravenously.[54] The response rate to binimetinib was 15% (including 1% complete response), and the median PFS was 2.8 months, compared with 1.5 months on dacarbazine (HR 0.62, 95% CI 0.47–0.80, $P<.01$). The median OS was similar in both arms. The response rate was similar (16%) in patients previously treated with immunotherapy. Binimetinib may represent an option for patients with progressive disease after front-line immunotherapy, especially in the absence of other targetable mutations or availability of clinical trial.

ABERRATIONS IN *KIT* IN MELANOMA

Melanomas harboring mutations in *BRAF* tend to occur in nonchronically sun-damaged skin. These mutations are uncommon in other histologic subtypes of melanoma, including acral-lentiginous, mucosal, and those arising in skin with chronic sun damage. Curtin and colleagues[55] analyzed 102 primary melanomas from these sites and discovered amplifications within a narrow band on chromosome 4q12, identifying a mutation in *K642E*, which is known to be oncogenic; this is also found in gastrointestinal stromal tumors (GIST).[56] These specimens also had elevations in KIT protein, which is a type III transmembrane RTK, thus identifying a link between *KIT* mutations and melanoma development.[57] It is now well known that *KIT* mutations can cause melanomas in mucosal regions, acral skin, and skin with sun damage.[55,58,59] *KIT*-activating mutations have been reported in 21% of mucosal melanomas, 11% of acral melanomas, 16.7% of melanomas in chronically sun-damaged skin, and 15% of anal melanomas.[55,60] The most common *KIT* mutations in melanoma are L676P and K642E translocations.[61] Imatinib mesylate is a specific inhibitor of the *bcr-abl* tyrosine kinase and is effective for the treatment of GIST and chronic myelogenous leukemia.[59] Approximately 70% of *KIT* mutations occur in the juxtamembrane region, which is a predictor of responsiveness to imatinib.

Since the identification of *KIT* mutations in melanoma, several trials have been performed to identify patients most likely to benefit from KIT inhibition. Imatinib was the first targeted drug identified to have therapeutic activity against *KIT*-mutated melanoma given its use in other malignancies harboring *KIT* mutations. Early demonstration of clinical activity of *KIT* inhibitors was published in case reports using imatinib and dasatinib.[62] Initial studies of imatinib failed to demonstrate efficacy, likely secondary to nonselection of specific molecular subtypes of melanoma more apt to harbor the target of interest.[63–65]

In an enriched population of *CKIT* mutant and/or amplified melanoma, Carvajal and colleagues[66] reported a 16% (4/25 evaluable patients) durable response rate. The median time to progression was 12 weeks, and median OS was 46.3 weeks. The 4 patients who achieved durable responses maintained disease control for more than 1 year. Guo and colleagues[67] performed a phase 2 trial of imatinib in China. Forty-three patients were evaluated with a reported ORR of 23.3% and median PFS of 3.5 months. Overall 1-year survival rate was 51%, and disease control rate (DCR) was 53.5%. Patients who experienced a partial response (PR) had significantly longer PFS and OS compared with patients with stable disease (9 vs 1.5 months; 15 vs 9 months, respectively). Patients who progressed were allowed to escalate the imatinib dose from 400 mg daily to 800 mg daily, but of these 15 patients, only 1 patient achieved stabilization of disease, whereas the others experienced progression. Hodi and colleagues[68] performed a third phase 2 trial of imatinib with 24 evaluable target-enriched melanoma patients. The trial cohort included 8 patients with *KIT* mutations, 11 with *KIT* amplifications, and 5 with both. They reported a best ORR of 29%; responses were only seen in patients harboring *KIT* mutation and not in those with *KIT* amplifications. Median time to progression was 3.7 months, and overall DCR was 50%.

These trials suggest that durable responses may be seen in *KIT* mutant melanoma treated with imatinib. Unfortunately, most patients eventually progress. The reported median times to disease progression of approximately 3 months in these target-enriched trials are significantly lower than time to progression when imatinib is used to treat GIST (median time to progression of 18 months).[68] It is unclear why there is such a difference in response between *KIT*-mutant melanoma and GIST, despite the presence of the same mutation, suggesting that there may be other pathways involved in treatment resistance that require further elucidation.

Nilotinib is another selective *bcr-abl* tyrosine kinase inhibitor similar in structure to imatinib.[69] In a phase 2 trial of nilotinib in 42 melanoma patients with *KIT* mutations, amplifications, or both, a response rate of 16.7% and DCR of 57.1% was reported. The median duration of response was 34 weeks. Most responses were again seen in patients with *KIT* mutations (6/7) rather than *KIT* amplification (1/7).

There are several ongoing studies of other novel KIT inhibitors in melanoma. PLX3397 (Pexidartinib) is being evaluated in 2 trials; the PIANO (PLX3397 KIT in Acral aNd mucOsal Melanoma) trial will investigate its efficacy in *KIT*-mutant acral and mucosal melanoma (NCT02071940). Another phase 1/2 study of this agent is underway in Asia (NCT02975700), first to determine the recommended phase 2 dose and then to assess its efficacy in patients with unresectable or metastatic *KIT*-mutated melanoma. Another novel agent under investigation is regorafenib, which is already approved for the treatment of metastatic colorectal,[70] GIST,[71] and hepatocellular carcinoma.[72] Regorafenib is a multikinase inhibitor, and the investigators propose that this will provide better efficacy in *KIT*-mutated melanomas (NCT02501551).

SUMMARY

The understanding of the pathways involved in melanoma development is essential to identifying therapeutic targets. Understanding of the MAP kinase pathway has led to successful therapeutic targeting of the *BRAF V600* mutation, accounting for 50% of melanomas arising from skin without chronic sun damage. Results for exploiting *NRAS and CKIT* mutations as valid targets have been less successful, underscoring the need to understand dominant mechanisms of melanomagenesis and resistance to therapy, whether primary or acquired. Moving the use of effective systemic therapy to earlier stages of disease may result in higher cure rates from melanoma. Trials combining targeted therapy with immunotherapy either concurrently or sequentially are currently ongoing. Results from these and other biomarker-driven trials will help shape the future armamentarium in localized and advanced melanoma, aiming to achieve a personalized therapy based on the molecular signature of an individual tumor.

DISCLOSURE

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REFERENCES

1. Goldinger SM, Murer C, Stieger P, et al. Targeted therapy in melanoma-the role of BRAF, RAS and KIT mutations. EJC Suppl 2013;11(2):92–6.
2. Nikolaou VA, Stratigos AJ, Flaherty KT, et al. Melanoma: new insights and new therapies. J Invest Dermatol 2012;132(3 Pt 2):854–63.
3. Sullivan RJ, Flaherty KT. Resistance to BRAF-targeted therapy in melanoma. Eur J Cancer 2013;49(6):1297–304.
4. Shtivelman E, Davies MQ, Hwu P, et al. Pathways and therapeutic targets in melanoma. Oncotarget 2014;5(7):1701–52.
5. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417(6892):949–54.
6. Tsao H, Chin L, Garraway LA, et al. Melanoma: from mutations to medicine. Genes Dev 2012;26(11):1131–55.
7. Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. Cell 2015;161(7):1681–96.
8. Munoz-Couselo E, Adelantado EZ, Ortiz C, et al. NRAS-mutant melanoma: current challenges and future prospect. Onco Targets Ther 2017;10:3941–7.
9. Dankort D, Curley DP, Cartlidge RA, et al. Braf(V600E) cooperates with Pten loss to induce metastatic melanoma. Nat Genet 2009;41(5):544–52.
10. Tsao H, Mihm MC Jr, Sheehan C. PTEN expression in normal skin, acquired melanocytic nevi, and cutaneous melanoma. J Am Acad Dermatol 2003;49(5):865–72.
11. Zhou XP, Gimm O, Hampel H, et al. Epigenetic PTEN silencing in malignant melanomas without PTEN mutation. Am J Pathol 2000;157(4):1123–8.

12. Stahl JM, Sharma A, Cheung M, et al. Deregulated Akt3 activity promotes development of malignant melanoma. Cancer Res 2004;64(19):7002–10.
13. Klein A, Sagi-Assif O, Meshel T, et al. CCR4 is a determinant of melanoma brain metastasis. Oncotarget 2017;8(19):31079–91.
14. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364(26):2507–16.
15. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. Ann Oncol 2017;28(10):2581–7.
16. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15(3):323–32.
17. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380(9839):358–65.
18. Broman KK, Dossett LA, Sun J, et al. Update on BRAF and MEK inhibition for treatment of melanoma in metastatic, unresectable, and adjuvant settings. Expert Opin Drug Saf 2019;18(5):381–92.
19. Long GV, Flaherty KT, Stroyakovskiy D, et al. Dabrafenib plus trametinib versus dabrafenib monotherapy in patients with metastatic BRAF V600E/K-mutant melanoma: long-term survival and safety analysis of a phase 3 study. Ann Oncol 2017;28(7):1631–9.
20. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372(1):30–9.
21. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. Lancet Oncol 2016;17(9):1248–60.
22. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;19(5):603–15.
23. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med 2014;371(20):1877–88.
24. Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015;386(9992):444–51.
25. Robert C, Grob JJ, Stroyakovskiy D, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med 2019;381(7):626–36.
26. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371(20):1867–76.
27. Dummer R, Ascierto PA, Gogas HJ, et al. Overall survival in patients with BRAF-mutant melanoma receiving encorafenib plus binimetinib versus vemurafenib or encorafenib (COLUMBUS): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2018;19(10):1315–27.
28. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous Melanoma, Version 2.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2019;17(4):367–402.
29. Faries MB, Thompson JF, Cochran AJ, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med 2017;376(23):2211–22.

30. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017;377(19):1813–23.
31. Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. J Clin Oncol 2018;JCO1801219. https://doi.org/10.1200/JCO.18.01219.
32. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377(19):1824–35.
33. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378(19):1789–801.
34. Amaria RN, Prieto PA, Tetzlaff MT, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. Lancet Oncol 2018;19(2):181–93.
35. Long GV, Saw RPM, Lo S, et al. Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, BRAF(V600) mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. Lancet Oncol 2019;20(7):961–71.
36. Eroglu Z, Eatrides J, Naqvi SMH, et al. Neoadjuvant BRAF-targeted therapy in regionally advanced and oligometastatic melanoma. Pigment Cell Melanoma Res 2019. https://doi.org/10.1111/pcmr.12813.
37. Amaria RN, Menzies AM, Burton EM, et al. Neoadjuvant systemic therapy in melanoma: recommendations of the International Neoadjuvant Melanoma Consortium. Lancet Oncol 2019;20(7):e378–89.
38. Tawbi HA, Boutros C, Kok D, et al. New era in the management of melanoma brain metastases. Am Soc Clin Oncol Educ Book 2018;38:741–50.
39. Frinton E, Tong D, Tan J, et al. Metastatic melanoma: prognostic factors and survival in patients with brain metastases. J Neurooncol 2017;135(3):507–12.
40. Sloot S, Chen YA, Zhao X, et al. Improved survival of patients with melanoma brain metastases in the era of targeted BRAF and immune checkpoint therapies. Cancer 2018;124(2):297–305.
41. Izraely S, Klein A, Sagi-Assif O, et al. Chemokine-chemokine receptor axes in melanoma brain metastasis. Immunol Lett 2010;130(1–2):107–14.
42. Fazakas C, Wilhelm I, Nagyoszi P, et al. Transmigration of melanoma cells through the blood-brain barrier: role of endothelial tight junctions and melanoma-released serine proteases. PLoS One 2011;6(6):e20758.
43. Klein A, Schwartz H, Sagi-Assif O, et al. Astrocytes facilitate melanoma brain metastasis via secretion of IL-23. J Pathol 2015;236(1):116–27.
44. Berghoff AS, Rajky O, Winkler F, et al. Invasion patterns in brain metastases of solid cancers. Neuro Oncol 2013;15(12):1664–72.
45. Xie TX, Huang FJ, Aldape KD, et al. Activation of stat3 in human melanoma promotes brain metastasis. Cancer Res 2006;66(6):3188–96.
46. Adler NR, Wolfe R, Kelly JW, et al. Tumour mutation status and sites of metastasis in patients with cutaneous melanoma. Br J Cancer 2017;117(7):1026–35.
47. Harding JJ, Catalanotti F, Munhoz RR, et al. A retrospective evaluation of vemurafenib as treatment for BRAF-mutant melanoma brain metastases. Oncologist 2015;20(7):789–97.
48. Villanueva J, Vultur A, Lee JT, et al. Acquired resistance to BRAF inhibitors mediated by a RAF kinase switch in melanoma can be overcome by cotargeting MEK and IGF-1R/PI3K. Cancer Cell 2010;18(6):683–95.

49. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol 2017;18(7):863–73.
50. Puzanov I, Amaravadi RK, McArthur GA, et al. Long-term outcome in BRAF(V600E) melanoma patients treated with vemurafenib: patterns of disease progression and clinical management of limited progression. Eur J Cancer 2015;51(11):1435–43.
51. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13(11):1087–95.
52. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. Ann Oncol 2017;28(3):634–41.
53. Ascierto PA, Schadendorf D, Berking C, et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 2013;14(3):249–56.
54. Dummer R, Schadendorf D, Ascierto PA, et al. Binimetinib versus dacarbazine in patients with advanced NRAS-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 2017;18(4):435–45.
55. Curtin JA, Busam K, Pinkel D, et al. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24(26):4340–6.
56. Isozaki K, Terris B, Belghiti J, et al. Germline-activating mutation in the kinase domain of KIT gene in familial gastrointestinal stromal tumors. Am J Pathol 2000;157(5):1581–5.
57. Yarden Y, Kuang WJ, Yang-Feng T, et al. Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J 1987;6(11):3341–51.
58. Patrick RJ, Fenske NA, Messina JL. Primary mucosal melanoma. J Am Acad Dermatol 2007;56(5):828–34.
59. Hodi FS, Friedlander P, Corless CL, et al. Major response to imatinib mesylate in KIT-mutated melanoma. J Clin Oncol 2008;26(12):2046–51.
60. Antonescu CR, Busam KJ, Francone TD, et al. L576P KIT mutation in anal melanomas correlates with KIT protein expression and is sensitive to specific kinase inhibition. Int J Cancer 2007;121(2):257–64.
61. Abbaspour Babaei M, Kamalidehghan B, Saleem M, et al. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. Drug Des Devel Ther 2016;10:2443–59.
62. Woodman SE, Trent JC, Stemke-Hale K, et al. Activity of dasatinib against L576P KIT mutant melanoma: molecular, cellular, and clinical correlates. Mol Cancer Ther 2009;8(8):2079–85.
63. Wyman K, Atkins MB, Prieto V, et al. Multicenter phase II trial of high-dose imatinib mesylate in metastatic melanoma: significant toxicity with no clinical efficacy. Cancer 2006;106(9):2005–11.
64. Kim KB, Eton O, Davis DW, et al. Phase II trial of imatinib mesylate in patients with metastatic melanoma. Br J Cancer 2008;99(5):734–40.
65. Ugurel S, Hildenbrand R, Zimpfer A, et al. Lack of clinical efficacy of imatinib in metastatic melanoma. Br J Cancer 2005;92(8):1398–405.
66. Carvajal RD, Antonescu CR, Wolchok JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;305(22):2327–34.

67. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 2011;29(21):2904–9.
68. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 2013;31(26):3182–90.
69. Guo J, Carvajal RD, Dummer R, et al. Efficacy and safety of nilotinib in patients with KIT-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol 2017;28(6):1380–7.
70. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381(9863):303–12.
71. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381(9863):295–302.
72. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;389(10064):56–66.