Targeted Therapies for Cutaneous Melanoma

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KEYWORDS

• Melanoma • Targeted therapy • MAPK signaling • BRAF • MEK • NRAS

KEY POINTS

- The molecular characterization of melanomas for BRAF, NRAS, and KIT mutations is increasingly essential for the optimal selection of targeted therapies and clinical trials in patients with advanced disease.
- In melanomas with BRAF V600 mutations, both RAF-inhibitor and MEK-inhibitor monotherapy improves overall survival. Resistance to both drug classes invariably develops but may be potentially delayed by upfront combination therapy.
- NRAS-mutant disease is more refractory to targeted therapy, although MEK-inhibitor monotherapy appears promising, and combination strategies are under investigation.
- KIT inhibitors are active in melanomas with exon-11 and exon-13 KIT mutations, with several compounds undergoing randomized phase III studies.

INTRODUCTION

Melanoma is the most deadly form of skin cancer, accounting for more than two-thirds of skin cancer–related mortality.[1] Although most patients with localized disease can be cured with complete surgical excision, melanoma is highly malignant, and even small primary tumors have the potential to metastasize.[2] In those who develop disseminated disease, treatment options have been limited. Melanoma has long been proved to be refractory to conventional chemotherapeutics.[3] Dacarbazine has been considered the standard treatment for patients with metastatic melanoma for more than 30 years, yet only 5% to 15% of patients will achieve a response and no overall survival benefit has ever been demonstrated.[4] Comparative trials of dacarbazine with other cytotoxic agents such as temozolomide, fotemustine, or platinum-based regimens, or in combination with biological agents such as interferon-α2b or

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high-dose interleukin-2, have failed to improve on this benchmark.[4] During this era, the median survival for patients with metastatic melanoma was between 6 and 9 months.[2]

Only more recently have tangible advances in the treatment of metastatic melanoma been realized. Developments in understanding of immune checkpoint regulation and the molecular biology of melanoma have laid the groundwork for 2 distinct treatment approaches that culminated in the successful phase III clinical trials of ipilimumab and vemurafenib in 2011.[5,6] Ipilimumab is an antibody directed against the inhibitory cytotoxic T-lymphocyte associated antigen 4 (CTLA-4) receptor expressed by activated T cells. Disruption of this immune checkpoint mechanism results in an enhanced T-cell–mediated antitumor response. In phase III studies, treatment with ipilimumab was associated with modest response rates and improvements in median overall survival, but a notable 10% improvement in overall survival after 2 and 3 years of follow-up.[6] A subsequent analysis has demonstrated that this plateau in melanoma-related deaths is maintained from 3 years out to beyond 10 years after ipilimumab therapy, suggesting that a proportion of patients will develop truly durable antitumor responses.[7] Risks associated with ipilimumab include a 15% to 20% incidence of clinically significant autoimmunity. Next-generation antibodies targeting the interaction between another negative regulator of T-cell function, programmed cell death 1 (PD-1) receptor and its ligand, appear more specific for T-cell anticancer immunity and may be associated with a higher response rate and less frequent autoimmune effects.[8,9] A more thorough review of immunologic therapies in melanoma is provided elsewhere in this issue.

This article focuses on the second approach: the clinical development of specific targeted therapies in direct response to the recent discoveries characterizing common oncogenic drivers in cutaneous melanoma. In particular, mutations resulting in the constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, a key regulator of normal cellular growth and proliferation, appear to be central to the pathogenesis of most melanomas. Vemurafenib was the first of several agents now proven to target this pathway in cutaneous melanoma.

THE MITOGEN-ACTIVATED PROTEIN KINASE PATHWAY IN CUTANEOUS MELANOMA

Extracellular ligands bind to specific membrane-bound receptor tyrosine kinases (RTKs) to initiate MAPK signaling. Subsequent recruitment and activation of the guanosine triphosphatase (GTPase), RAS, results in a cascade of phosphorylation (activating) events involving the serine/threonine kinases RAF, MEK, and ERK. Active ERK phosphorylates numerous cytoplasmic and nuclear targets regulating processes such as cell proliferation, differentiation, survival, migration, and angiogenesis (**Fig. 1**).[10]

ERK has been demonstrated to be hyperactivated in most melanomas. The most commonly identified abnormality is a mutation in *BRAF*, with a frequency of 40% to 60%.[11–13] A single valine for glutamine substitution at codon 600 (V600E) accounts for greater than 75% of *BRAF* mutations,[11] with the resultant protein having a 10-fold greater kinase activity than wild-type BRAF.[14] *NRAS* mutations occur in about 15% of melanomas and are mutually exclusive to *BRAF* mutations.[13,15] Other mutations, for instance in *KIT* (encoding the KIT RTK), have been identified but are far less common.[15] However, the relative frequencies of different genetic mutations appear to cluster with certain clinicopathologic features: whereas *BRAF* mutations are most common in melanomas arising in skin without evidence of chronic sun damage, in much rarer mucosal or acral melanomas *BRAF* mutations are uncommon but the frequency of *KIT* mutations ranges from 10% to greater than 20%.[15–17] These findings allow for more rationalized mutation testing, and have resulted in a shift from the