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<p>The last 30 years has seen a revolution in melanoma. Fundamental elements of the surgical, adjuvant medical, and systemic therapy for the disease have been significantly altered toward improved management and better outcomes. The intent of this article is to reflect on past efforts and research in melanoma and the current landscape of treatment of melanoma. The authors also hope to capture the excitement currently rippling through the field and the hope for a cure. The intent of treatment of advanced melanoma, which was once considered incurable, has changed from palliative to potentially curative.</p>	
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<p>From 1976 to 2010, only 2 medications were approved for treating metastatic melanoma. Between 2011 and 2013, 4 agents were approved and other therapies have shown great promise in clinical trials. Fundamental discoveries, such as the identification of oncogenic mutations in most melanomas, the elucidation of the molecular signaling resulting from these mutations, and the revelation that several cell surface molecules serve as regulators of immune activation, have been instrumental in this progress. This article summarizes the molecular pathogenesis of melanoma, describes the current efforts to target oncogene-driven signaling, and presents the rationale for combining immune and molecular targeting.</p>	
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<p>Surgery remains the mainstay of treatment of every patient in whom complete excision of all disease is feasible. For clinically localized melanoma (clinical stages 0–II), wide excision and, when appropriate, sentinel lymph node biopsy are well established. The management of stage III melanoma is more contentious. Resection remains the first choice of therapy for patients with oligometastatic melanoma in accessible locations, but careful consideration of preoperative use of highly active drugs is appropriate. Decisions regarding surgical management of stage IV melanoma should routinely be made in the context of a multidisciplinary team approach.</p>	
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<p>Adjuvant therapy targets melanoma micrometastases in patients with surgically resected disease that carry a high risk of death from melanoma recurrence. In this setting, adjuvant therapy provides the greatest</p>	

opportunity for cure before progression into advanced inoperable stages. In randomized clinical trials, interferon-alfa has been shown to have a significant impact on relapse-free survival and, at high dosage, on overall survival compared with observation (E1684) and the GMK vaccine (E1694). This article reviews melanoma adjuvant therapy along with the ongoing and planned clinical trials.

Targeted Therapies for Cutaneous Melanoma

491

Damien Kee and Grant McArthur

Melanoma is resistant to cytotoxic therapy, and treatment options for advanced disease have been limited historically. However, improved understanding of melanoma driver mutations, particularly those involving the mitogen-activated protein kinase pathway, has led to the development of targeted therapies that are effective in this previously treatment-refractory disease. In cutaneous melanomas with *BRAF* V600 mutations the selective RAF inhibitors, vemurafenib and dabrafenib, and the MEK inhibitor, trametinib, have demonstrated survival benefits. Early signals of efficacy have also been demonstrated with MEK inhibitors in melanomas with *NRAS* mutations, and KIT inhibitors offer promise in melanomas driven through activation of their target receptor.

Treatments for Noncutaneous Melanoma

507

Danny N. Khalil and Richard D. Carvajal

Historically the approach to treating noncutaneous melanoma was largely guided by the experience with cutaneous melanoma, particularly in the metastatic setting. However, as genetic tools have allowed clinicians to better characterize these malignancies, their unique biology has become apparent. The ability to accurately distinguish the subtypes of melanoma and the genetic alterations that drive them is beginning to yield the tools that are shifting this disease from one that has proved to be intractable in the advanced setting to one that can be effectively treated.

Targeted Therapy Resistance Mechanisms and Therapeutic Implications in Melanoma

523

Guo Chen and Michael A. Davies

Although selective mutant *BRAF* inhibitors have revolutionized the treatment of metastatic melanoma, the magnitude and duration of their clinical benefit are significantly undermined by *de novo* and acquired resistance. Functional studies, molecular characterization of clinical samples, and clinical trials are providing insights into the landscape of resistance mechanisms in this disease. These findings have implications for the development of rational therapeutic approaches, and have identified several challenges that remain to be overcome if outcomes are to be improved in patients with metastatic melanoma.

Introduction to the Role of the Immune System in Melanoma

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Kim Margolin

The concept of immunosurveillance of cancer has been widely accepted for many years, but only recently have the precise mechanisms of

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