

Preface

Cracking the Melanoma Nut

For decades, melanoma has retained a reputation as one of the last major tumor types to lack any therapy shown to improve patient survival in the metastatic setting. The standard chemotherapeutic agent, dacarbazine, was approved in 1976, and the immunotherapeutic agent IL-2 was FDA approved in 1998. However, neither drug traversed the hurdle of a randomized phase III clinical trial. Dozens of chemotherapeutic agents, and more recently signal transduction inhibitors, have been shown to have insignificant clinical activity in phase II clinical trials. Combination chemotherapy has been shown to be no better than single agent dacarbazine, and combined delivery of chemotherapy plus IL-2-based immunotherapy has been reported to offer no additional survival benefit compared to chemotherapy alone. Melanoma also is known to be relatively resistant to standard regimens of ionizing radiation. Based on these facts, it is not difficult to suggest that the traditional empiric oncology drug development paradigm has essentially failed when applied to the treatment of patients with melanoma.

Excitingly, this situation is in the midst of a tremendous change, and that change has been catalyzed by significant advances in fundamental and translational science. Genomic technologies have enabled the identification of driver oncogene mutations in specific kinases that are present in defined subsets of melanoma. These mutated kinases are now targetable with kinase inhibitors which are having potent clinical activity. In addition, tremendous advances in our understanding of immune regulation, with insights derived from analysis of patient material in search for mechanisms of tumor resistance to immune attack, have led to novel therapeutic approaches designed to overcome these barriers and tip the balance toward immune-mediated tumor destruction. While these are still early days, these new discoveries are likely to lead to the FDA approval of several new agents for the treatment of melanoma in 2011 – on the heels of a dry spell of two approvals in 35 years!

This volume, *Targeted Therapeutics of Melanoma*, aims to present the state-of-the-art information driving the clinical pursuit of agents that target either specific oncogenic

pathways that contribute directly to melanoma growth, or immunoregulatory processes that enable tumor escape from immune attack. It is fully anticipated that perseverance to understand additional molecular details of key events that drive melanoma growth will lead to continued development of novel targeted therapies to improve even further the clinical outcome of patients with this disease.

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