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Gajewski TF, Hodi FS. Targeted Therapeutics in Melanoma. New York: Springer, 2012

Reviews by Lynn A. Cornelius, M.D., Mark A. Hurt, M.D.

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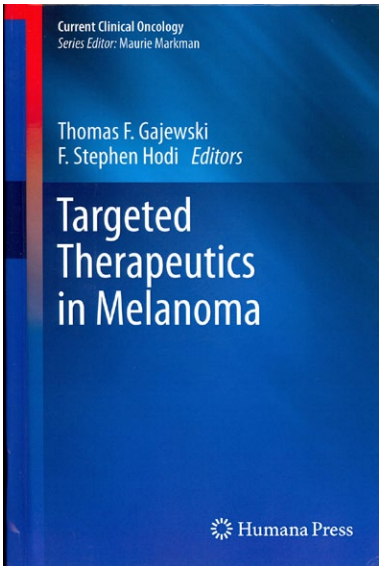

Gajewski TF, Hodi FS. Targeted Therapeutics in Melanoma. New York: Springer, 2012. 337 pp.; ISBN 978-1-61779-406-3; UPC 9781617794063; $219.

Review by Lynn A. Cornelius, M.D.

Targeted Therapeutics in Melanoma, Gajewski and Hodi (eds.), is one of a series of publications from *Current Clinical Oncology* that provides up-to-date information regarding new developments in cancer diagnosis and treatment provided by experts in the respective specialty fields. This volume, with a focus on melanoma, delivers just that, with an impressive list of international contributors. The title may be somewhat misleading, as the book covers mutation-, anti-angiogenesis- and immune-targeted therapies equally well. It serves as an excellent resource for physicians who, in any specialty, diagnose and treat melanoma patients.

For anyone familiar with melanoma, it is clear that the landscape is rapidly evolving. Melanoma has been long recognized as a disease that, once widely metastatic, is nearly uniformly fatal. Conventional chemotherapy has been disappointing, and despite the recognition that melanoma is one of the more immunogenic of tumors, the effectiveness of previous treatments targeting immune modulation has been meager, at best. In a few short years, however, we have gone from discovery in the laboratory to more effective, although not yet universally curative, treatments. Furthermore, with the application of each new therapy in tandem with on-going basic science investigations, we are gaining more insight into the biology and the mutational drivers of this disease.

Overall, the book is organized in a very logical manner, although it is also formatted such that the reader can easily locate information that is specific and stand-alone in a particular area of interest. The contents are segregated into three parts: Part I, Advances in Melanoma Biology, serves as an introduction into melanoma genomics, molecular targets and predictive biomarkers in the disease. Part II, Signaling Molecules as Molecular Targets, includes background information on molecular pathways that are relevant to melanoma biology, the rationale for targeting specific molecules, and a relatively current synopsis of clinical trials to date. Part III, Rational Immunotherapy Approaches in Melanoma, similarly addresses the known immunobiology of melanoma to date, and the underlying principles for specific immune-modulating treatments—those in current use in the clinic and others in clinical trial. A few of the chapters in Parts II and III are somewhat dense (in the authors' attempts to describe complex tumor and system biology), but this does not detract from the take-away message. The corollary to this point is that any reader familiar with the subject matter will, most likely, still glean additional insight into the topic. Many of the chapters have informative illustrations and tables.

One note is that the book has more typographical and formatting errors than would be expected in a formal pub-

lication. This can be slightly distracting, but may reflect the current content and timeliness of the publication.

As someone who is familiar with the field, I feel this is an excellent resource and reference for physicians and scientists who want a comprehensive overview of current advances in melanoma therapy. I truly appreciate the opportunity to provide this review.

Lynn A. Cornelius, M.D. is Winfred A. & Emma R. Showman Professor of Dermatology and Chief of the Division of Dermatology at Washington University School of Medicine St. Louis, MO, USA. Contact Dr. Cornelius at: LCorneli@dom.wustl.edu.

Comments by Mark A. Hurt, M.D.

I thank Dr. Cornelius for her constructive review. I contacted the book's editors, but neither replied to my enquiry. I extend the opportunity for them to respond to Dr. Cornelius or to me.

This book is 377 pages, including the index. As the title states, it is a tome targeted toward the targeted therapy of melanoma, not the diagnosis as such. This fact alone serves to remove it from the daily experience, currently, of many, if not most, dermatopathologists. This is a book for physicians who treat patients with an established diagnosis of melanoma.

The Editors begin in their Preface with the depressing fact that the FDA, from 1976 until 2011, approved only two forms of non-surgical therapy—these include dacarbizine, approved in 1976, and IL-2, approved by the FDA in 1998. They continue, however, that genomic technologies have been the source of newer information on oncogene mutations that have led to the knowledge of kinases present in some melanomas. This reviewer wonders what advances *might* have been made on this front without the heavy-hand of FDA approval that has violated the rights of patients and physicians in attempting heroic advancements in the treatment of melanoma.

The editors divide this book into three parts: the first addresses advances in the understanding of the biology of melanoma; the second explores signaling molecules as molecular targets; the third grapples with immunotherapeutic approaches in the treatment of melanoma. All of the chapters are written as though they were stand-alone articles, each with an abstract, body, and conclusion.

Of note to dermatopathologists, there has been difficulty in finding correlation with the model of so-called melanoma "progression" as advocated by Clark et al (1984) [1] to the genomics of melanoma. Kashini-Sabet, in chapter 2 (Melanoma Genomics), rightly states that "while this model of melanoma progression was described several years ago and is well understood, prior to the advent of microarray analysis, one would be hard pressed to identify genes whose differential expression corresponded to any of these phases of melanoma progression." This is not at all surprising given that the "progression" hypothesis was dubious from the very beginning, and I take issue that anyone ever understood it. There is no credible evidence that melanocytic nevi "transform" into melanomas; cells transform, but lesions do not. What is readily observable is that there are nevi, nevi in conjunction with melanomas, and melanomas. How a melanocyte eventually becomes a melanoma is as much an enigma today as it was when Clark et al wrote their article in 1984. It is true that much new information about certain genes associated with melanomas, but this is not the same as knowing the cause(s) of melanoma.

The editors, in Part II, organize the discussion of signaling molecules as molecular targets for the treatment of melanoma. These articles center on KIT, B-Raf inhibition, the Notch and β-Catenin pathways, STAT3 and Src Signaling, TOR, P13K & AKT Pathways, antiapoptotic pathways, and antiangiogenesis therapy.

Immunotherapeutics, discussed in Part III, include melanoma antigens recognized by T lymphocytes, melanoma vaccines, adoptive cell therapy for treatment of metastatic melanoma, anti-CTLA-4 monoclonal antibodies, anti PD-1 and anti B7-H1/PD-L1 monoclonal antibodies, agonist immune costimulatory agents, novel cytokines, and modulation of the tumor environment.

Ultimately, this technical work requires a considerable base of knowledge to understand and apply. I think the appeal of it is for those melanoma oncologists and dermatologists with a strong focus on the medical treatment of advanced melanoma. This is particularly true for patients with melanomas that have evolved beyond the surgical stages. I suspect, in the next few years, dermatopathologists will find a role in the assistance of dermatologic oncologists who use these therapies to treat patients with advanced melanoma. In the meantime, dermatopathologists might want to purchase this book as a point of reference, as these foci of research and treatment are only the beginning of what promises to be an explosion of possible treatments for patients with melanoma.

Reference

1. Clark WH Jr, Elder DE, Guerry D 4th, Epstein MN, Greene MH, Van Horn M. A study of tumor progression: the precursor lesions of superficial spreading and nodular melanoma. Hum Pathol 1984 Dec;15(12):1147-65. PubMed PMID: 6500548.

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