Melanoma Prevention, Detection, and Treatment: Where We Stand, Where We’re Headed

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Despite the best efforts of scientists worldwide, melanoma research over much of the past decade has had a Shakespearean feel – considerable sound and fury, but not ultimately signifying much in terms of reducing incidence or saving lives. Excitement has always appeared a hair’s breadth away, with investigations in all directions hot on the trail of answers but not quite attaining them, knocking on the doors but not quite opening them.

Now, many doors are swinging wide. Helped mightily by scientists’ growing ability to explore changes on the genetic, genomic, and molecular levels, the past two years have seen giant strides in most areas of melanoma investigation, from prevention, detection, and diagnosis to staging and (most spectacularly) treatment. Patients are at last starting to reap the benefits, and hopes for many more significant breakthroughs in the near future are soaring.

From the Editors

In the past couple of years, melanoma research has gone into hyperdrive. After many frustrating decades watching incidence soar and too many patients die, the efforts of countless scientists worldwide are coming to fruition, offering tangible benefits here and now as well as remarkable promise for the future. This is true in virtually every area of endeavor across the entire spectrum of melanoma investigation, from epidemiology and prevention to diagnosis, staging, and treatment.

Thanks to new and improved detection methods, tumors are being discovered earlier, when much more treatable, and discoveries at the molecular and genetic levels are giving us a far greater understanding of the underpinnings of different melanomas, leading to more targeted treatment methods that are finally giving patients with advanced disease a fighting chance for delayed recurrence and even extended overall survival.

Normally in The Melanoma Letter, we invite experts to provide succinct, probing analyses of their recent work or other topics relevant to the melanoma community. However, given the recent accelerated pace of developments in the field, we have strayed a bit from our usual format in this current issue, taking it upon ourselves to present a general overview of the current state of the art of melanoma research. We hope that this will provide some perspective on the broad range of exciting developments in our field, and set the stage for more focused, in-depth stories anticipated from our colleagues later this year and beyond.

As a final note, we would like to offer our profound gratitude to Alfred W. Kopf, MD, one of the founding editors of this publication, who has remained a valued member of the editorial staff since its inception in 1983 – about a third of his life, as he recently pointed out to us. Now Professor Emeritus of Dermatology at New York University School of Medicine, Dr. Kopf is choosing to step down as Consulting Editor of The Melanoma Letter, a position he has held since 1991, helping to shape every single issue we have published. While we respect his decision to embrace retirement more fully, we are very sorry to lose the benefit of his knowledge, experience, prestige, and wisdom. Our appreciation for his unparalleled impact on the publication, Dr. Kopf will remain on the masthead as Editor Emeritus. Dr. Kopf, we will sorely miss the opportunity to interact with you on a regular basis. Our very warmest regards and best wishes.

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Associate Editor
Epidemiologic Trends

Over the past decade, melanoma incidence has continued to soar, with a dramatic rise in both invasive and in-situ melanoma.\(^1\)\(^,\)\(^3\) In 2010, an estimated 68,130 invasive melanomas and 46,770 in-situ melanomas were diagnosed in the United States.\(^4\)

Some concern has been expressed that rising cancer incidence in general may partly reflect “overdiagnosis,” a phenomenon that occurs when detection pressure (somewhat akin to a police force prodded to produce a murder suspect) results in diagnosis and treatment of cancers that would, if left undetected, not eventuate in harm to the patient.\(^5\) The potential problem with overdiagnosis is unnecessary cost and morbidity. The truth is, we have worked hard in recent years to make both the public and physicians aware of the early warning signs of melanoma, promoting regular self-examination and yearly professional examination, and using terms such as the “ABCDs” (asymmetry, border irregularity, color variegation, and diameter greater than 6mm) as visual shorthand aids to boost melanoma suspicion and recognition. This may translate to some overdiagnosis, with excision of in-situ melanomas, atypical moles, and other lesions that might never advance to full-blown invasive melanoma. However, given the grave consequences of discovering melanomas too late, it is hard to support giving less education to the public and medical professionals.

Furthermore, fashion and recreation trends leading to increased ultraviolet sun exposure and tanning bed use are likely the major driving force behind the melanoma epidemic. Recent research, in fact, has clearly linked melanoma with a pattern of intermittent, intense UV exposure, of the kind associated with regular indoor work and sun-drenched vacations.\(^5\) Plus, multiple studies in the past few years have convincingly linked tanning bed use to melanoma, as well as to squamous and basal cell carcinoma.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^9\)

Concurrent with the rise in melanoma incidence has been a significant albeit less dramatic rise in melanoma mortality.\(^10\) Over the past three decades melanoma mortality has risen most dramatically in men, especially those over age 50. During this same period, there has been a small decrease in melanoma mortality in younger individuals, especially in women.\(^2\) However, there has also been a disturbing rise in incidence in younger people; melanoma is now the most common form of cancer for young adults 25-29 years old and the second most common form of cancer for young people 15-29 years old.\(^11\) This trend is especially pronounced in women. Between 1980 and 2004, annual melanoma incidence among young women increased by 50 percent, from 9.4 cases to 13.9 cases per 100,000 women.\(^3\) Women aged 39 and under have a higher probability of developing melanoma than any other cancer except breast cancer.\(^12\) The fact that melanoma incidence in young women has risen substantially, while mortality has gone down, could suggest that they haven’t yet accepted the importance of reducing UV exposure (they are the most frequent users of tanning booths, for example),\(^13\) but many may have absorbed the lessons of early detection.

Prevention

The Role of UVR Damage

Ultraviolet radiation exposure remains the only known preventable cause of melanoma. While not all MMs are caused by UVR, its etiologic role in the majority of melanomas is supported by substantial epidemiologic and basic science data.\(^6\)\(^,\)\(^7\)\(^,\)\(^8\)\(^,\)\(^15\) However, until recently, this role has been largely inferential, without direct evidence of UV-induced mutations in melanoma; the evidence of a link between UVR, actinic keratosis, and squamous cell carcinoma had been better established. However, in 2010, researchers at Wellcome Trust Sanger Institute in Hinxton, UK, published the first study sequencing the entire genome of a metastatic melanoma, revealing it to be teeming with UV signature mutations. The predominant location of these mutations in the intergenic regions of the chromosomes explains why they may have been missed in prior studies, which focused on mutations in putative cancer genes.\(^14\) While it is not clear to what extent UVR influences the development of different melanomas, the study appears to provide the strongest case ever that some melanomas are caused by UVR. This link was reinforced by a companion study of a patient’s lung cancer genome; just as the vast majority of mutations in the melanoma genome were caused by UV damage, the majority of the mutations in the lung cancer genome were caused by cigarette smoking.

Sunscreen

Similarly, direct evidence has been lacking for effective melanoma prevention through sun protection. Until last year, the best evidence came from epidemiological studies, such as the large case-control study of women in San Francisco by Cress and Holly.\(^15\) However, this changed in 2010, with publication of the long-term follow-up of the relatively large Nambour (Queensland) sunscreen trial in Australia – the first randomized clinical trial to compare regular sunscreen users (a group trained to use sunscreen daily) against a control group (a discretionary group allowed to continue using or not using sunscreen as they always had). The results demonstrated the significant impact of (SPF 16) sunscreen use on the incidence of invasive melanoma.\(^16\) Ten years after the trial’s completion, 11 new primary melanomas were observed in the daily sunscreen group versus 22 in the discretionary group, a statistically significant 50 percent reduction in melanoma incidence. (HR 0.50, 95% CI, 0.24 to 1.02; P=.051). For invasive melanoma, the differences were even greater – 3 cases occurring in the daily sunscreen group versus 11
in the discretionary group (HR 0.27; 95% CI, 0.08 to 0.97). The scientists acknowledge that further research is needed on larger groups, but consider their results convincing enough to recommend daily sunscreen application.

Despite extensive public health efforts to decrease UV exposure, recent data suggest continued high rates of sunburn, tan-seeking, and tanning bed use, especially among young women. While public education efforts have stressed the importance of sun-protective clothing and shade-seeking, sunscreens remain the preferred method of sun protection for the majority of Americans. In the past, this presented a problem, because sunscreens offered far more complete protection in the UVB than in the UVA spectrum; even sunscreens that boasted “broad-spectrum” protection failed to protect fully against UVA I and/or UVA II. Thus, people relying solely on sunscreen were still significantly exposed to damaging rays.

In the past several years, however, UVA protection has continually evolved, with ingredients such as stabilized avobenzone, micronized zinc oxide and titanium dioxide, and emulsions added to the mix. The current generation of sunscreens offers excellent UVB/UVA protection. [See “The New Seal of Recommendation,” p. 6.]

While some groups, most notably the self-proclaimed “consumer watchdog” Environmental Working Group, have raised questions regarding the safety of sunscreen ingredients such as oxybenzone, retinyl palmitate, and micronized titanium dioxide and zinc oxide, the current data support the excellent safety profile of all available FDA-approved sunscreens. 17

**At Last: the FDA’s Final Regulations on Sunscreen**

The US Food and Drug Administration (FDA) had long complicated matters by failing to finalize its monograph on sunscreen labeling. This decades-long delay led to great confusion among American consumers in making sunscreen choices. However, the new sunscreen regulations at long last have been approved. Announced to the public on June 14, they offer many significant steps forward in informing American consumers about what combination of sunscreen ingredients is both safe and effective for true broad-spectrum protection. [See “The Impact of the FDA Final Regulations on Sunscreen,” below.]

Unfortunately, the FDA’s deliberate pace continues to deprive the US of newer ingredients, such as Tinosorb®B, already available in Europe and elsewhere. Tinosorb®B (bisoctizole), Tinosorb®S (bemotrizonol), octyl triazone, amiloxate, enzacamene, and isocotrizol all are currently under FDA consideration.

Just as sunscreens have significantly improved, so have other forms of sun protection, with innovations such as 99 percent UV-blocking sunglasses and window film, high-UPF clothing, and a wide array of shade structures and shade devices adding to our safety options. When advising patients, it is important to remind them that sunscreen is just one vital part of a comprehensive daily sun protection regimen.

The growing public health effort to prevent melanoma and other skin cancers has led to increasing controversy about vitamin D. The vitamin is essential for bone health, and basic science and epidemiologic studies suggest that it may also have a role in prevention of heart disease, cancer, and a host of other ailments. This has led to dramatic increases in vitamin D testing and supplementation in the US and has caused some authors to indict sun protection as a public health risk. An extensive review by the International Agency for Research on Cancer (IARC) concluded that the data does not support any form of intentional UV exposure to promote vitamin D production. 18 Similarly, an extensive report in late 2010 by the Institute of Medicine (IOM) found insufficient data to suggest...
changing the current recommended serum levels of vitamin D. There is, however, growing recognition among melanoma experts of the importance of recommending adequate vitamin D supplementation to all patients, especially those assiduously using sun protection. The IOM recommendations for supplementation are presented in Table I.

**Detection and Diagnosis**

There is general consensus that early detection offers the greatest opportunity for reducing melanoma mortality in the short-term. However, in the absence of randomized clinical trials demonstrating the efficacy of melanoma screening, the United States Preventive Services Task Force does not recommend screening for the general public. Many organizations, including the American College of Preventive Medicine, do recommend it for high-risk individuals, including those with many moles and a family history of melanoma. Accordingly, enhancement of early detection has taken twin paths: increasing and improving total-body self-examination (TBSE) by the public while enhancing the diagnostic accuracy of physicians, who are often faced with identifying needle-in-a-haystack melanomas occurring in the background of numerous atypical moles.

**Patient Self-Detection**

For decades, change in the color, shape, or size of a pigmented lesion has been recognized as a sensitive warning sign of melanoma. This significance has been recently reinforced with the addition of “E” (for evolving or change) into the ABCD acronym for early melanoma detection. Similarly, it has long been appreciated that melanomas typically stand out as different from the remainder of a patient’s spots. This public health message has been formalized as the “ugly duckling sign” of melanoma, representing an “outlier” lesion that looks significantly different than lesions around it; it is especially useful for recognizing nodular melanomas, which do not usually reflect the ABCDE signs.

To disseminate these public health messages, the melanoma community is faced with the challenges and opportunities presented by the ubiquitous internet and general culture of information overload. With innumerable media outlets, it is a challenge to ensure reaching the public at large with accurate information. At the same time, in today’s connected society, the public has the opportunity to access extensive illustrations and in-depth descriptions of skin self-examination and the warning signs of melanoma.

**Physician Diagnosis**

In the realm of physician diagnosis, the trend has been to leverage technology and physician extenders in an attempt to improve diagnostic accuracy. The mainstay technologies for melanoma diagnosis include dermoscopy and its more technologically advanced offshoots for assessment of individual lesions, and total-body photography (TBP) to identify changing lesions in patients with numerous atypical nevi. After sluggish initial adoption of dermoscopy by American dermatologists, its use in clinical practice has recently grown dramatically. The value of total-body photography as a baseline in tracking existing moles, new moles, and other skin changes is intuitively appreciated by the high-risk patient with numerous nevi, and the recent advent of digital imaging systems (such as MoleMap CD™ and MIROR™ DermaGraphix) for acquiring and archiving total-body skin images has resulted in greater dissemination.

Many other exciting technologies are being developed as potential aids in melanoma diagnosis – from high-resolution ultrasound and confocal scanning laser microscopy to computer-assisted diagnostic devices with fully automated analysis systems. These automated systems rely on analysis of optical, acoustic, electrical, and/or molecular signals to differentiate between melanoma and benign lesions or other malignancies. The first of these to seek FDA approval is a multispectral imaging system called MelaFind® that, in preliminary studies, demonstrated better diagnostic accuracy than dermatologists. However, the FDA advisory panel that reviewed the data recommended approval by the narrowest of margins, and to date, many months after the public panel hearing, the FDA has not yet issued a verdict on approval. The major concern raised was that while the device’s sensitivity exceeded that of expert dermatosists in the narrow context of the clinical trial, it might lead to missed cases of melanoma in routine clinical practice. An additional concern was that given its reported specificity, application of the device to inadequately pre-screened lesions would lead to many unnecessary biopsies.

Regardless of the outcome of this particular review, it can be anticipated that new technological aids to melanoma detection and diagnosis will

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<th>Age (years-old)</th>
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<th>Calcium RDA* (mg/day)</th>
<th>Vitamin D RDA* (IU**/day)</th>
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<td></td>
<td>700</td>
<td>600</td>
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<td>19-50</td>
<td>Males</td>
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<td>51-70</td>
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<td>51-70 Females</td>
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<td>&gt;18 Pregnant/lactating</td>
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*RDA: Recommended Dietary Allowance  **International Units

**TABLE 1. Dietary Reference Intakes for Calcium and Vitamin D**

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reach market in the near-to-intermediate future. As with TBP, significant logistic, cultural, and financial hurdles will need to be solved before broad adoption of these technologies. The impact on public health, however, will likely be worth the effort and wait. For example, it has already been demonstrated that expert dermoscopists can dramatically reduce unnecessary biopsies without impacting sensitivity of melanoma diagnosis.30 Hopefully, these new technologies will improve melanoma diagnosis without promoting epidemic overdiagnosis.

**Staging**

While designed primarily for research purposes, the American Joint Committee on Cancer (AJCC) melanoma staging system has dramatic implications for patient care. Patients rely heavily on it to gauge their prognosis, and most therapeutic algorithms are stage-driven. Ongoing refinements are designed to home in on prognostically distinct, homogeneous subsets of a melanoma population.

The most recent iteration of the staging system has added mitotic rate (mitoses/mm²) as an important prognostic variable. Primary melanoma thickness and tumor ulceration continue to define T category strata, with a mitotic rate of at least 1 mitosis/mm² replacing Clark’s level of invasion as a primary criterion defining the T1b subcategory.31 (Table 2) In determining N subcategories, the presence of nodal micrometastases can now be defined using either hematoxylin & eosin (H&E) or immunohistochemical staining, whereas previously only H&E could be used. Furthermore, based on the consensus that volumes of regional metastatic tumor even less than 0.2mm in diameter (previously used as the lower threshold defining nodal metastasis) are clinically significant, nodal tumor deposits of any size now define the presence of regional nodal metastasis. And finally, staging of metastatic melanoma from an unknown primary site has been clarified; patients with mets arising in lymph nodes, skin, or subcutaneous tissues without a known associated primary melanoma are all categorized as stage III, not stage IV.

**Therapy**

*Management of Primary and High-risk Melanoma*

The surgical management of melanoma consists primarily of what should now really be termed “modest” rather than “wide” local excision of the primary lesion, with less disfiguring 1-2cm margins recommended in recent years, compared to the 3-5cm protocol of the past.

For poorly circumscribed lentigo maligna melanomas in cosmetically sensitive areas, modified versions of margin-controlled, staged surgical excision techniques such as Mohs micrographic surgery, using immunostained frozen sections and/or rush permanent sections, have been increasingly applied with good results in the hands of experienced practitioners. Similarly, many cases of surgically challenging borderline lentiginous melanocytic dysplasias and lentigo malignas have been successfully treated with topical imiquimod informed by generous surveillance and post-therapy biopsies. While these approaches are not supported by randomized control trials and do not supplant standard surgery as front-line therapy, they have significantly expanded therapeutic considerations for these patients.32

The current staging system assumes the widespread use of sentinel lymph node biopsy (SLNB) for higher-risk melanoma as an aid to prognosis.33 However, in the absence of conclusive, compelling data that SLNB saves lives, the indications for SLNB remain somewhat controversial. This is especially true in older age groups where comorbidities abound and SLNB is often negative among patients who go on to die of their disease. The role of SLNB is also controversial at the other

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**TABLE 2: TNM Staging Categories for Cutaneous Melanoma**31,42

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<tr>
<td><strong>Tumor</strong></td>
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<td>• Thickness</td>
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<td>• Ulceration</td>
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<td>• Clark Level</td>
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<td><strong>Nodes</strong></td>
<td><strong>Nodes</strong></td>
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<td>• Number of involved LN**</td>
<td>• Number of involved LN**</td>
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<td>• Macrometastasis</td>
<td>• Macrometastasis</td>
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<td>• Micrometastases defined by H&amp;E staining</td>
<td>• Micrometastases defined by H&amp;E or immunohistochemical staining</td>
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<tr>
<td>• Satellite or in-transit metastases</td>
<td>• Satellite or in-transit metastases</td>
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<tr>
<td><strong>Metastasis</strong></td>
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<tr>
<td>• Site(s) of distant metastasis</td>
<td>• Site(s) of distant metastasis</td>
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<tr>
<td>• Serum LDH level</td>
<td>• Serum LDH level</td>
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<tr>
<td><strong>Site(s) of distant metastasis continue to define the M category. Patients with metastatic melanoma arising in lymph nodes, skin, or subcutaneous tissues without a known associated primary melanoma will now all be stage III, not stage IV.</strong></td>
<td><strong>Site(s) of distant metastasis continue to</strong></td>
<td><strong>Increased serum LDH level continues as an adverse predictor of survival.</strong></td>
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*AJCC: American Joint Committee on Cancer
**LN: Lymph nodes
H&E: Hematoxylin and eosin staining
end of the age spectrum, where positive nodes are common in association with atypical spitzoid tumors, despite excellent survival rates for these SLNB-positive patients. Across the entire age spectrum, the clinical utility of complete lymph node dissection for patients with a positive SLNB remains a question awaiting the future results of the MSLT-II trial (Multicentre Selective Lymphadenectomy Trial 2).

In 2011, a notable advance was also made in adjuvant therapy for high-risk patients, with FDA approval of peginterferon alfa-2b (aka Sylatron) for stage III melanoma patients with lymph node involvement. This subcutaneously injected cytokine, which stimulates immunity, is the first adjuvant for stage III patients approved since high-dose interferon alfa-2b (IFN alfa-2b) in 1995. Approval followed a single Phase III trial, EORTC 18991, in which melanoma patients taking Sylatron remained relapse-free an average nine months longer than patients not taking the drug (34.8 months vs. 25.5 months)

The New Seal of Recommendation

Since 1979, The Skin Cancer Foundation’s Seal of Recommendation Program has been helping consumers select the safest and most effective sunscreen products. It is the only labeling program worldwide that not only sets rigorous standards for sun protection products, but scrupulously verifies they are met. Now, just as sunscreens have improved, so has the Seal of Recommendation. The Foundation has introduced several key innovations to the program that will be completed by mid-2012. In addition to new sunscreen standards, including rigorous ultraviolet A (UVA) protection requirements, the Foundation is launching a new labeling system classifying sunscreens as either “Daily Use” or “Active,” depending on their intended purpose.

The FDA’s sunscreen requirements serve only as rating and labeling guidelines. In contrast, the Foundation’s updated Seal will require scientific verification of each sunscreen’s UVA-protective and UVB-protective abilities. Additionally, there will now be two Seals of Recommendation – one called Daily Use and one called Active.

“Daily Use” products are intended to protect consumers from incidental sun exposure that occurs over short periods of time, during activities such as shopping and short drives. Examples of such sunscreen products might include daily moisturizers, cosmetics, foundations, eye creams and lip products. “Daily Use” products must have:

- An SPF (sun protection factor) of 15 or higher
- Validation of the SPF number by testing on 20 people
- A critical wavelength of 370 or Persistent Pigment Darkening (PPD) of 5 (both are measures of UVA protection) as tested on 10 people
- Acceptable results for phototoxic reactions and contact irritancy testing on 20 people
- Proof of photostability
- Substantiation for any claims that a sunscreen is water- or sweat-resistant.

“Active” products are designed to protect consumers from extended sun exposure and during recreational activities such as outdoor sports, picnics and pool parties. Examples might include sport sunscreens and baby products. “Active” products must have:

- An SPF of 30 or higher
- Validation of the SPF number by testing on 20 people
- A critical wavelength of 370 or Persistent Pigment Darkening (PPD) of 10, as tested on 10 people
- Acceptable results for phototoxic reactions and contact irritancy testing on 20 people
- Proof of photostability
- Proof of water resistance

The transition to the new Seal program will be complete by May 2012. Until then, the more than 1,000 products that currently carry the Seal of Recommendation may display either one of the new Seals or the traditional Seal.

The Seal of Recommendation program enables the Foundation to educate consumers when they are making important decisions about sun protection that directly affect their skin health. The program has set the standard for safe, effective, and photostable sun protection products, including sunscreens, sunglasses, sun-protective clothing, specially treated auto and residential window film, shade umbrellas, and more.

The Foundation’s volunteer Photobiology Committee, whose physician members are experts in the study of the interaction between ultraviolet (UV) radiation and the skin, reviews all the safety and efficacy data for every product before it can be awarded the Seal. The members of the Photobiology Committee are chairman Warwick L. Morison, MD, professor of dermatology, Johns Hopkins Medical School, Green Spring, Maryland; Henry W. Lim, MD, chairman and Clarence S. Livingood Chair, Department of Dermatology, Henry Ford Hospital, Detroit; John Epstein, MD, clinical professor of dermatology, University of California at San Francisco; Heidi Jacobe, MD, assistant professor of dermatology, University of Texas Southwestern Medical Center at Dallas, and Steven Q. Wang, MD, director, Dermatology Service, Memorial Sloan-Kettering Cancer Center, West New York, New Jersey.
months). However, there was no difference in overall survival. Patients with less advanced disease and fewer lymph nodes involved showed the greatest benefit. Efficacy appears similar to that of IFN alfa-2b, but the drug is easier to administer and produces fewer severe adverse reactions.

Management of Advanced Melanoma: Quantum Leaps in Systemic Therapy

Far and away the most exciting development in melanoma in the past year or two has been the promising results observed with targeted therapy for advanced disease. After decades of frustration and failure, new therapies are delaying recurrence and extending life by months or even years for many patients, in a few cases virtually curing them.

These therapies have capitalized on two major scientific advances: a) recently recognized driver mutations among subsets of melanoma newly characterized by molecular and genetic findings; and b) breakthroughs in our understanding of immunology in general and tumor immunology in particular.

It had been 13 years since the FDA last approved a drug [high-dose Interleukin-2] to treat advanced melanoma, a brutal disease with an average survival on the order of six months. IL-2 was approved after some success in a small minority of patients, producing complete responses in 10 percent of those treated, with 60 percent of those patients remaining disease-free after 5 years. Unfortunately, high-dose IL-2 remains associated with extensive multiorgan toxicity, severely limiting its use.

However, 2010 and 2011 have brought two major new options—both with jaw-dropping results in Phase I, II, and III trials. The sight of dozens of tumors shrinking in a matter of weeks in melanoma patients on the BRAF inhibitor PLX4032, developed by Plexxikon in partnership with Roche, spurred “pinch me” moments for researchers, the New York Times reported last year in a multi-part series, and another drug, ipilimumab, produced less dramatic but equally impressive benefits.

The sight of dozens of tumors shrinking in a matter of weeks in advanced melanoma patients on the BRAF inhibitor PLX4032 spurred “pinch me” moments for researchers.

The majority of melanomas arising in intermittently sun-exposed skin harbor an identical mutation in the BRAF gene, which PLX4032 (an oral kinase inhibitor now also variously known as vemurafenib, RG7204, or RO5185426) has successfully targeted. PLX4032 zeroes in on the V600 BRAF mutation, and in the first clinical trial on advanced melanoma patients with this mutation, it shrank tumors in an unparalleled 81 percent; no more than 20 percent typically respond to most other current drugs. Subsequently, a published Phase II study and a recently announced, but as yet unpublished, multicenter Phase III study have confirmed extended progression-free survival as well as significantly extended overall survival compared to patients on dacarbazine, with responses lasting from two to more than 18 months. Preliminary Phase III results were presented formally in June at the American Society of Clinical Oncology’s (ASCO) annual meeting, and Plexxikon has already submitted applications to the FDA and the European Medical Agency for regulatory approval. While the drug is undergoing the approval process, Genentech and Plexxikon are making PLX4032 available to patients with BRAF V600 mutation-positive melanoma through a global patient access program, and plan to continue to study the drug (and other prospective BRAF inhibitors, such as GSK2118436) in combination with other treatments.

Ipilimumab, a monoclonal antibody developed jointly by Medarex and Bristol-Myers Squibb, uses a broader approach, taking the brakes off the immune system so that it can fight cancer more aggressively. In one study, ipilimumab nearly doubled the number of patients surviving one year. It is the rising star of a class of agents called immune “checkpoint” inhibitor therapies that work by blocking the innate negative feedback of the immune system. By binding to the CTLA-4 checkpoint and inhibiting it from functioning, it gives the immune system freer rein to identify and eliminate melanoma cells. In a large Phase III trial of 676 advanced, inoperable melanoma patients published in 2010 in the New England Journal of Medicine, subjects previously treated unsuccessfully with other agents who received ipilimumab or ipilimumab plus a melanoma vaccine (gp100) lived on average 32 percent longer and had a 20 percent greater chance (45 percent vs. 25 percent) of surviving one year than those who received gp100 alone. Twenty-four percent were alive after two years, compared with just 14 percent of those treated with the other therapy, making ipilimumab the first treatment ever to improve overall survival in advanced melanoma patients.

In its latest study findings, ipilimumab increased overall survival in inoperable stage III or stage IV metastatic melanoma patients who had not received prior therapy. The study specifically showed that ipilimumab combined with the chemotherapydacarbazine increased overall survival, while dacarbazine alone did not. These latest findings, like those for PLX4032, were presented at ASCO’s annual meeting in June. According to the best estimates, ipilimumab may offer many patients a 2-year survival advantage, with a smaller percentage being virtually cured. In late March ipilimumab, under the trade name Yervoy™, became the newest drug to be approved by the FDA for treatment of advanced metastatic melanoma.

Other exciting drugs are also in the pipeline. For example, the KIT inhibitor imatinib mesylate has shown great promise in a small subset of advanced melanoma patients with a mutated KIT gene. Although three small initial studies showed no significant anti-
tumor effect, they did not require the presence of a KIT mutation in patients. In newer trials that enrolled only patients with active KIT mutations, 20 to 30 percent treated achieved a major response. A 2010 Phase II study from China reported not only high response rates but prolonged progression-free survival.11

Next Generation
As we move forward, optimizing treatment will require a personalized approach based upon understanding and targeting the underlying genetics of each patient and tumor. Studies combining Imilimumab, PLX4032, and imatinib with chemotherapy, various immunologic therapies, and other novel “targeted” treatments are ongoing. There is a great deal of anticipation that several such agents will find their way to market in the near future, leading to dramatic and sustained responses if not cures. While there is still a long path to travel to find the ultimate cure for metastatic melanoma, these and other developing drugs represent a significant step forward.

References