Despite the continuous challenges and questions that skin cancer poses to dermatologists, the therapeutic outlook appears to be improving. Over the last several years, new research has delved into the genetic factors of melanoma and clarified links between UV exposure and melanoma and other skin cancers. In addition, several newly approved and investigational therapies are targeting specific pathways and offering patients more options for managing disease. As we look to 2014 and consider the future of skin cancer research and treatment, it is important to keep informed regarding the latest therapeutic trends while never losing sight of boosting awareness for prevention efforts. Ahead are some trends in research and treatment that are worth noting.

**NON-MELANOMA SKIN CANCER**

While surgical methods likely represent the most common and reliable form of therapy for most non-melanoma skin cancers (NMSC), several new advances are changing how physicians can approach many NMSCs. Among these is the approval of vismodegib (Erivedge, Genentech), which targets the hedgehog-signaling pathway in cells, and has been found effective in the treatment of late-stage basal cell carcinomas (BCC). Since vismodegib was approved based on a single, non-randomized trial, continued data have evaluated both the safety and efficacy of the agent. In a recent study, patients with advanced BCC received 150mg vismodegib daily until disease progression or intolerable toxicity. Patients were treated for a median of 5.5 months. Objective responses occurred in 46.4 percent of locally advanced BCC (laBCC) and 30.8 percent of patients with metastatic BCC (mBCC). Although these data support the safety and efficacy of vismodegib, studies are currently underway to assess long-term outcomes and predictors of response.

Elsewhere in the realm of BCCs, the utility of topical therapies continues to grow. Photodynamic therapy, while not a first-line therapy, has shown varying degrees of efficacy, while topical 5-fluorouracil and imiquimod have been shown to be efficacious and safe for the treatment of superficial basal cell carcinoma (BCC) but not other BCC subtypes or squamous cell carcinoma (SCC).

This past year, more literature supported the use of Picato (ingenol mebutate, LEO Pharma) gel (0.015% and 0.05%) to effectively treat actinic keratoses in just two or three days. Since there is no way to predict which actinic keratosis will advance to skin cancer, early treatment of lesions is critical. In Phase III clinical trials, 60-68 percent of patients with AKs on the face and scalp and 44-55 percent with AKs on the trunk and extremities saw a 75 percent or greater reduction in existing lesions with Picato. Complete clearance rates ranged from 28-42 percent (the trunk and extremities) to 37-47 percent (face and scalp). The most common side effects of Picato are skin redness, flaking/scaling, crusting, and swelling.

There are fewer promising avenues in the treatment of squamous cell carcinoma currently, but several targeted agents are worth following. For example, erlotinib (Tarceva) and gefitinib (Iressa) both target EGFR proteins, which are produced on the surfaces of SCCs and presumably help them grow. They are both in clinical trials right now, along with dasatinib (Sprycel), which targets different cell proteins and is being studied for advanced skin cancers.
MELANOMA: DETECTION AND TREATMENT

While melanoma is a continued treatment challenge, the FDA approvals of two new oral therapies this year—dabrafenib (Tafinlar, GlaxoSmithKline) and trametinib (Mekinist, GlaxoSmithKline)—represent a potentially new threshold in melanoma care. Dabrafenib is the second BRAF inhibitor approved for melanoma, after vemurafenib (Zelboraf, Genentech). It has demonstrated efficacy in patients with BRAF mutant melanoma, but more recently, the BREAK-MB trials have shown evidence of disease activity in patients with metastatic melanoma brain metastases and potential abrogation of BRAF inhibitor resistance.

Trametinib is an oral mitogen-activated protein kinase (MEK) inhibitor that has also been found to be effective. One recent study assessed the potential of trametinib in combination with gemcitabine for advanced solid tumors and showed good efficacy results. The authors noted that while most toxicities were manageable, the addition of trametinib may possibly increase gemcitabine-associated myelosuppression. Thus, they recommended that future studies of this combination will require monitoring to maintain dose and schedule. A New Zealand study recently compared responses of melanoma cell lines to MEK and BRAF inhibitors and found that cell lines sensitive to vemurafenib were also sensitive to trametinib. These findings support the notion that MEK inhibitors might be combined with BRAF inhibitors in the treatment of melanomas with activated BRAF. Moreover, given the high sensitivity to trametinib of some lines with wildtype BRAF status, the study indicates that MEK inhibitors could have a therapeutic effect against some melanomas as individual agents. The data for both dabrafenib and trametinib are still somewhat limited, but they have each shown encouraging enough efficacy to secure approvals and will continue to be examined under a variety of circumstances.

Apart from treatment, other advances in testing and detection are changing how researchers and clinicians are classifying and approaching skin melanoma. Earlier this year, a non-invasive gene expression profile test (DecisionDx-Melanoma) from Castle Biosciences was validated as a strong, independent predictor of metastatic risk for classifying Stage I or II cutaneous melanoma tumors. The study indicates that MEK inhibitors could have a therapeutic effect against some melanomas as individual agents. The data for both dabrafenib and trametinib are still somewhat limited, but they have each shown encouraging enough efficacy to secure approvals and will continue to be examined under a variety of circumstances.

Another development last year has been the continued discussion of the melanoma detection device MelaFind. MelaFind received FDA approval in November 2011, but it should still be considered to be in the developmental stage. The MelaFind pivotal study was the largest positive prospective clinical study ever conducted in melanoma detection with 1,384 patients presenting 1,831 stage. The MelaFind pivotal study was the largest positive prospective clinical study ever conducted in melanoma detection with 1,384 patients presenting 1,831 skin lesions. The aim of the study was to establish the safety and effectiveness of MelaFind using sensitivity and specificity as metrics. MelaFind successfully met both set endpoints. It demonstrated 98.3 percent sensitivity by correctly identifying 172 out of 175 melanomas and high-grade lesions. Dermatologists detected 72 percent of melanomas in the study. The median Breslow thickness of invasive melanomas in the pivotal study was 0.365mm and 45 percent of all melanomas were in situ indicating melanomas tested were clinically challenging and in a treatable stage. MelaFind was more specific than dermatologists in the study; MelaFind demonstrated 10.8 percent specificity vs. 5.6 percent dermatologist specificity.

However, while MelaFind can analyze small pigmented spots identified by dermatologists as having signs of melanoma, it is not designed to evaluate other problems: large melanomas, colorless melanomas, or two other types of skin cancer—basal and squamous cell carcinoma. Some biostatisticians are also critical of MelaFind, saying the device can recognize a high percentage of melanomas correctly because it also falsely scores as positive so many non-melanoma lesions—potentially prompting unneces-

“As science continues to shed light on skin cancer, it is our job to follow through and re-enforce to patients the importance of UV avoidance.”
sary biopsies. Certainly this device is a tool to be utilized, but with the clinical data, as uncertain as it is in the setting of high costs and the current lack of CPT coding, suggest the long term future for MelaFind is cloudy as we head into 2014.

PREVENTION IS THE BEST TREATMENT

The recent breakthroughs in the research and treatment of various forms of skin cancer offers encouragement that we are moving toward better and more reliable models of detection and care. And while we can only hope that 2014 will feature the same steady flow of new developments, we can never lose sight of our role as educators in the larger effort to prevent skin cancer.

Last month, when it was revealed that actor Hugh Jackman was treated for a basal cell carcinoma on his nose, the actor noted on his Instagram account, "Please don’t be foolish like me. Get yourself checked. And use sunscreen!"

The influence of celebrities can be significant, and while Jackman may have opened the eyes of thousands of people to the hazards of skin cancer, the onus is on us as clinicians to promote sun-smart behavior and encourage routine screenings. As science continues to shed light on skin cancer, it is our job to follow through and re-enforce to patients the importance of UV avoidance. ■

Jonathan Wolfe, MD is a Clinical Associate Professor of Dermatology at the University of Pennsylvania in Philadelphia, PA where he is on the staff of the Pigmented Lesion Clinic. He is also Division Head of Dermatology at Einstein Montgomery Hospital in East Norriton, PA and maintains a private practice in Plymouth Meeting, PA.

1. Envedge Prescribing Information. www.envedge.com