SHH-MB tumors revealed that the location of genetic alterations along the SHH pathway plays a role: Loss-of-function mutations in PTCH1, which inhibits vismodegib sensitivity, as did alterations in p53. However, tumors with pathway mutations downstream of SMO, including GLI2 and SUFU, were nonresponsive.

“These results validate findings from larger genomics studies that showed substantial numbers of SHH-MB patients had varying mutations predictive of vismodegib response,” says Yoon-Jae Cho, MD, a pediatric neuro-oncologist at California’s Stanford University School of Medicine. There have been no previous pediatric trials with vismodegib, he adds, so these studies “open up our ability to combine vismodegib with other targeted therapies, or with some of the backbone chemotherapy regimens for kids, for more durable responses.”

Clinicians at St. Jude have now incorporated vismodegib into treatment regimens after patients with SHH-MB complete standard-of-care therapy. This could reduce recurrence, Robinson says; if not, new therapeutic targets may be uncovered by analyzing the molecular features of recurrent tumors.

“The idea is to look at vismodegib responses in a larger population of patients with SHH-MB,” Robinson explains. “The more specific our drugs, the better we need to understand the tumors we’re targeting.”

**Hedgehog Inhibitor Approved for BCC**

The FDA has approved a second targeted treatment for locally advanced basal cell carcinoma (BCC). Sonidegib (Odomzo; Novartis) inhibits a key step in the Hedgehog pathway, a developmental regulatory cascade that is aberrantly activated in the majority of BCCs.

BCC is the most common form of skin cancer, accounting for 80% of skin cancers in the United States. Most cases can be cured with surgery, radiation, or topical medications, but until recently there was no effective treatment for the small number (1%–10%) of inoperable, recurrent, and metastatic tumors. That changed in 2012 with the approval of vismodegib (Erivedge; Genentech), an inhibitor of the smoothened (SMO) protein, a component of the Hedgehog pathway.

The FDA approved sonidegib, another SMO inhibitor, based on results from the phase II BOLT study, which compared two doses (200 mg and 800 mg per day, given orally) in 194 patients with locally advanced BCC who were ineligible for surgery or radiation. Sonidegib showed durable antitumor activity, with 58% of the patients given the 200 mg dose achieving an objective response. Most side effects were mild to moderate, including muscle spasms, loss of sense of taste, and alopecia. Severe side effects included elevated creatine kinase levels and breakdown of muscle tissue. Because there was no evidence of better tumor response in the patients receiving the 800 mg dose of sonidegib, and adverse events were more common, the FDA approved the 200 mg dose.

“The clinical activity and side effect profile of sonidegib appear similar to vismodegib’s. Due to the importance of the Hedgehog pathway in fetal development, both drugs carry a black box warning about significant fetal toxicity.”

“With the approval of sonidegib, ‘we have two drugs that are very effective,’” says William Sharfman, MD, director of cutaneous oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore, MD. “The challenge now is to figure out which patients with locally advanced disease can best benefit from the drug,” he says.

Sharfman notes that the drugs might be useful to shrink tumors before disfiguring surgery or delay the need for surgery, and studies of these neoadjuvant applications are under way.

The downfall of many molecularly targeted therapies is the development of resistance. Clinical experience suggests that about 20% of patients taking vismodegib develop resistance within a year, mainly through acquired mutations in SMO. Whether sonidegib will perform better remains unknown, says Jean Y. Tang, MD, PhD, a dermatologist and physician-scientist at California’s Stanford University. Preliminary experience with the drugs suggests that cross-resistance does occur, says Tang.

Studies of sonidegib and other SMO inhibitors are also under way in medulloblastoma, another cancer caused by SMO mutations, as well as other tumors with Hedgehog pathway activation.

“The hope is that this pathway or target is relevant for other cancers and that one can expand the treatment options for other deadly cancers,” says Tang.

**Pinpointing Melanoma’s Invasive Trigger**

In its earliest stage, melanoma proliferates within a basal skin layer that separates the outer epidermis and inner dermis, but the disease is in situ, meaning melanoma cells aren’t yet invasive or metastatic. What provokes their aggression hasn’t been well understood; however, a recent study suggests that the surrounding microenvironment, along with Notch signaling, may be key (Mol Cell 2015;59:664–76).

“To metastasize, melanoma cells need to invade the dermis, which contains blood vessels,” explains senior author Carmit Levy, PhD, an investigator at Tel Aviv University’s Sackler School of Medicine in Israel. “Oddly, before heading deeper [into the dermis], they first extend upward, to the top of the epidermis. I wondered why they were apparently starting out in the wrong direction, and it occurred to me that our skin’s outermost layer might contain the trigger for invasion.”

Levy and her group explored their hunch by co-culturing noninvasive melanoma cells with different types of normal human skin cells, including differentiated and basal keratinocytes from the epidermis. Only melanoma cells interacting with differentiated keratinocytes became highly invasive—measured via a gel-based infiltration assay—and displayed reduced pigmentation, another marker of invasive capability. Mice treated with this combination of melanoma cells and
Hedgehog Inhibitor Approved for BCC