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so one therapeutic possibility might be to suppress lamins even more in the former. Again, the challenge would be finding ways to do so without affecting lamin levels in normal cells.

To better translate their findings into therapeutic opportunities, the researchers are now trying to learn more about the differences between migrating cancer cells and immune cells.

"We're looking at whether metastasizing cancer cells have special properties that help them deal with this scenario of repeated damage and repair," Lammerding says. Identifying such unique characteristics will enable the development of antimetastatic drugs that selectively target invasive cancer cells, instead of being "a sledgehammer that hits everything." *–Janet Colwell* ■

Pembrolizumab Yields Lasting Merkel Cell Carcinoma Responses

In a phase II single-arm study, the PD-1 checkpoint inhibitor pembrolizumab (Keytruda; Merck) produced durable responses in 56% of patients with advanced Merkel cell carcinoma (MCC), a disease for which there are no FDA-approved treatments. Although that response rate is on par with the response rate to standard treatment with platinum chemotherapy and etoposide, the study showed that pembrolizumab proved significantly superior in controlling the disease.

The findings were presented by Paul Nghiem, MD, PhD, head of dermatology at the University of Washington in Seattle, at the American Association for Cancer Research Annual Meeting 2016 in New Orleans, LA, April 16–20, and simultaneously published (N Engl J Med 2016 Apr 19 [Epub ahead of print]).

MCC afflicts 2,000 people in the United States each year, often appearing as fast-growing shiny skin lumps. Exposure to ultraviolet light is a risk factor, and the disease strikes more often in people over age 50 and individuals with a compromised immune system.

Merkel cell polyomavirus drives about 80% of cases. Discovered in 2008, this virus infects most people during childhood, but typically causes no problems. However, the unlikely acquisition of multiple genetic mutations

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Paul Nghiem, MD, PhD, reported that 56% of patients with Merkel cell carcinoma responded to pembrolizumab in a phase II trial, on par with standard treatment. However, the PD-1 inhibitor proved superior in controlling the disease.

enables the virus to evade immune system surveillance and trigger MCC. More than 40% of patients develop advanced MCC, and among those, roughly 90% die in less than a year.

Benefits of treatment with standard chemotherapy are short-lived, as about half of patients experience progressive disease within 3 months. Because previous research found that patients with MCC whose tumors showed evidence of a killer T-cell response fared better, researchers thought that pembrolizumab, which ramps up the immune system's response and has already been approved for the treatment of certain melanomas and lung cancers, might be worth a try.

Nghiem and colleagues enrolled 26 patients with advanced MCC who had not received prior systemic therapy; 17 had virus-positive disease. All received pembrolizumab every 3 weeks for up to 2 years, with tumor evaluations every 9 to 12 weeks.

Overall, among the 25 patients who had at least one radiologic assessment, 56% responded to the drug. That rate is nearly twice the response rate seen in melanoma, the first cancer for which this immunotherapy drug was approved, Nghiem said.

The response rate was higher in patients with virus-positive than virus-negative disease (63% versus 44%), although this difference was not statistically significant. Baseline tumor expression of PD-L1, the ligand of PD-1, did not predict response to pembrolizumab, Nghiem added.

Most notable, Nghiem said, was that 86% of the responders continued to respond to treatment after 6 months, on average, significantly longer than with chemotherapy. In addition, the initial 3-month evaluation seemed to indicate a patient's trajectory for the rest of the study, with benefits persisting for responders, and nonresponders continuing to worsen.

Aiming to confirm these results, Nghiem said his team will expand the trial to include 24 more patients. *—Esther Landhuis* ■

Patients with *NTRK* Fusions Respond to Targeted Therapies

In separate phase I trials, two investigational anticancer therapies—LOXO-101 (Loxo Oncology) and entrectinib (Ignyta)—showed dramatic clinical activity in patients with a variety of cancers in separate phase I trials, according to data presented at the American Association for Cancer Research (AACR) Annual Meeting 2016, held in New Orleans, LA, April 16–20.

Both drugs selectively inhibit a family of proteins called neurotropic tyrosine kinases, including TrkA, TrkB, and TrkC, which are overexpressed as a result of relatively rare gene fusions involving *NTRK1*, *NTRK2*, and *NTRK3*. Entrectinib also targets these proteins, as well as two fusion proteins encoded by translocations involving *ROS1* and *ALK*. All five proteins promote cancer cell proliferation and survival.

In November 2015, David Hong, MD, deputy chair and associate professor in the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston, reported on three patients with *NTRK* gene fusions enrolled in the LOXO-101 study, all of whom demonstrated partial responses to the treatment.

At the AACR meeting, Hong presented data on three more patients with *NTRK* fusions and noted that a seventh recently joined the study but has yet to be assessed. The seven have five different types of malignancy: sarcoma, papillary thyroid cancer, mammary analog secretory carcinoma (MASC) of the salivary glands, non–small cell lung cancer (NSCLC), and gastrointestinal stromal tumor. Five of the six evaluable patients had a partial response, while the sixth patient's tumor shrank by 18%. In addition, Hong said, brain metastases regressed significantly in one patient.

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