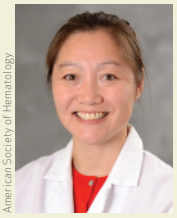
PEOPLE


American Society of Hematology

Stephanie Lee, MD, MPH, began a 1-year term as president of the American Society of Hematology (ASH) this month at the organization's 2019 Annual Meeting in Orlando, FL. She is a professor of oncology and medicine at the University of Washington and a member of the Fred Hutchinson Cancer Research Center in Seattle. Lee is also the research director of the Fred Hutchinson Long-Term Follow-Up Program, which tracks patients after bone-marrow or stem-cell transplants. Her research focuses on developing better ways to prevent, diagnose, and treat graft-versus-host disease.


American Society of Hematology

Also at the ASH meeting, **Richard A. Larson, MD,** professor of medicine and director of the Hematologic Malignancies Clinical Research Program at the University of Chicago in Illinois, won the Henry Stratton Medal for Clinical/Translational Research. His work has centered on understanding the genetic basis of leukemia and developing new therapies. As chair of what is now the Alliance for Clinical Trials in Oncology, Larson oversaw numerous leukemia trials. Larson has also served on the editorial boards of several journals.

MCLA-128 Fights *NRG1* Fusion–Positive Cancers

Three patients harboring *NRG1* fusions—two with pancreatic cancer and one with lung cancer—exhibited tumor shrinkage and improvement in symptoms when treated with Merus's bispecific antibody MCLA-128 (zenocutuzumab) in a clinical proof-of-concept study. Researchers reported the results at the 2019 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics in Boston, MA, October 26–30.

NRG1 fusions occur in less than 1% of cancers overall, but they are "enriched in diseases in desperate need of better therapy," such as *KRAS*–wild-type pancreatic ductal adenocarcinomas (PDAC) and invasive mucinous lung adenocarcinomas, said Alison Schram, MD, of Memorial Sloan Kettering Cancer Center (MSKCC) in New York, NY, who presented the findings. Directed against HER2 and HER3, MCLA-128 docks on HER2 and blocks NRG1-fusion binding to HER3, preventing downstream PI3K–AKT–mTOR signaling and inhibiting tumor-cell proliferation. It also engages the immune system by enhancing antibody-dependent cellular cytotoxicity.

Preclinical testing of MCLA-128 demonstrated its effectiveness in ovarian and breast cancer models harboring various NRG1 fusions, including *CLU–NRG1*, *TNFRSF10B–NRG1,* and *DOC4–NRG1* (Cancer Discov 2018;8:686–95).

Schram reported on three men who received MCLA-128 as part of an expanded access protocol. Two of them had *KRAS*–wild-type PDAC and had previously received chemotherapy, but the disease progressed. DNA sequencing revealed that they had *ATP1B1–NRG1* fusions, so they opted for MCLA-128.

The first patient experienced a partial response: Imaging showed a 54% reduction in tumor diameter after 5 months, and levels of CA 19-9, a biomarker for pancreatic cancer, decreased from 262 units/mL to 50 units/mL. (A normal level is less than 40 units/mL.) In addition, Schram noted that he regained weight and had improved quality of life. The second patient experienced stable disease, with a 25% reduction in tumor diameter; his CA 19-9 level dropped from 418 units/mL to 11 units/mL.

"Both patients remain on treatment 7-plus months into therapy and are tolerating it extremely well, with improvement in both disease-related symptoms and resolution of chemotherapy-associated toxicity," reported Schram.

The third patient had been diagnosed with non–small cell lung cancer (NSCLC). He received several chemotherapies and the HER2 inhibitor afatinib (Gilotrif; Boehringer Ingelheim), but the disease progressed. After DNA sequencing uncovered a *CD74–NRG1* fusion, he tried MCLA-128. He experienced a partial response, with a 41% decrease in tumor diameter after 4 months and improvement in brain metastases. He remains on treatment.

Research presented at earlier medical meetings found that less than 5% of 117 patients experienced grade 3 or 4 toxicity. Most side effects were mild, with diarrhea, weakness, fatigue, and nausea being the most common. None of the three patients with *NRG1* fusions treated at MSKCC experienced adverse events greater than grade 2.

The biggest limitation of the MSKCC research is the small number of patients. Although the researchers had identified 29 patients whose tumors carried *NRG1* fusions, several died before therapy could begin, and several more had localized disease and weren't eligible to receive the drug. However, based on their experience treating the three patients, researchers have launched a phase II basket trial of MCLA-128 in patients with *NRG1* fusion–positive PDAC, NSCLC, and other solid tumors. "We feel that this is a novel paradigm for targeting these rare genomic alterations," said Schram.

–Suzanne Rose ■

Trio Wins Nobel for Hypoxia Discoveries

Three scientists—William G. Kaelin Jr., MD, of Dana-Farber/Harvard Cancer Center in Boston, MA; Sir Peter J. Ratcliffe, MD, of the University of Oxford and the Francis Crick Institute in the UK; and Gregg L. Semenza, MD, PhD, of Johns Hopkins University School of Medicine in Baltimore, MD—won this year's Nobel Prize in Physiology or Medicine for their research elucidating how cells sense and adapt to changing oxygen levels—work that not only is fundamental to biology, but also has clinical applications for a range of diseases, including cancer.

"This is really a textbook finding," said Randall Johnson, PhD, of the University of Cambridge in the UK, who is a member of the Nobel Assembly. "This is one of the most basic mechanisms a cell has to adapt to its environment—to be able to counteract whatever oxygen levels it's encountering and … metabolically adjust to them."