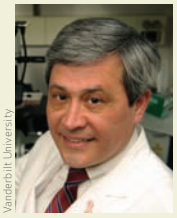
PEOPLE


Vanderbilt University

Breast cancer expert **Carlos Arteaga, MD,** began his new role as director of the Harold C. Simmons Comprehensive Cancer Center at The University of Texas Southwestern Medical Center in Dallas on September 1. Previously, Arteaga served as the director of the Center for Cancer Targeted Therapies, director of the breast cancer program, and associate director for translational and clinical research at the Vanderbilt-Ingram Cancer Center in Nashville, TN. A former president of the American Association for Cancer Research, Arteaga's research interests include gene signaling, molecular therapeutics, and drug resistance in breast cancer.

This month, **Steven D. Leach, MD,** will begin work as the director of the Norris Cotton Cancer Center at Dartmouth in Lebanon, NH. Most recently, Leach directed the Rubenstein Center for Pancreatic Cancer Research at Memorial Sloan Kettering Cancer Center in New York, NY. He has pursued multiple avenues of research on the disease, such as the mechanisms of development, the ability of molecular profiling to direct patient treatment, and the creation of organoid models to identify molecular pathways that correlate with the progression of pancreatic cancer.

Paul M. Harari, MD, director of the Department of Human Oncology at the University of Wisconsin School of Medicine and Public Health and the Carbone Cancer Center in Madison, will begin a 1-year term as president of the American Society for Radiation Oncology at the organization's annual meeting in San Diego, CA, at the end of the month. His research focuses on the treatment of head and neck cancer and how molecular signaling pathways can modulate tumor response to radiation.

Panel OKs CAR T Therapy for Leukemia

An expert panel recommended approval of Novartis's experimental chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel (CTL019), potentially ushering in a new standard of care for patients with advanced blood cancers. At a meeting on July 12, the FDA's 10-member Oncologic Drugs Advisory Committee voted unanimously in favor of approving the therapy to treat children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).

In making the recommendation, experts relied primarily on data from a single-arm phase II study in which 63 pediatric and young adult patients received tisagenlecleucel. After 3 months, 83% went into remission, and 75% remained disease-free after 6 months.

Although the FDA is not required to heed the panel's recommendation, it usually does so. A final decision on approval is expected by early October.

"Tisagenlecleucel is poised to become the first genetically modified T-cell therapy approved for cancer treatment," says Malcolm Smith, MD, PhD, associate branch chief for pediatric oncology at the NCI. "It provides another chance for children with relapsed/refractory ALL who previously had little or no chance for prolonged remissions."

The therapy involves harvesting patients' white blood cells and then shipping them to a manufacturing facility where T cells are isolated and genetically modified to express CARs that target CD19. Patients are then infused with their modified T cells, which grow and expand to potentially eradicate their cancer over 2 to 3 weeks.

"This treatment was remarkably effective in patients who had exhausted all other treatment options, including bone marrow transplants," says David Maloney, MD, PhD, of Fred Hutchinson Cancer Research Center in Seattle, WA. "It marks a whole new era for cancer therapy."

Despite the excitement surrounding CAR T-cell therapy, the field is still in its early stages, notes Smith. More clinical trials, as well as real-world data, are needed to better understand the short- and long-term risks and potential benefits of treatment.

"Tisagenlecleucel has a clear positive treatment effect in a substantial number of children with relapsed/refractory ALL, but more experience is needed to define the percentage of patients who attain complete, durable remissions," he says. "Researchers need to better understand the rates and severity of adverse events such as neurotoxicity, and whether there are long-term detrimental effects in some patients."

CAR T therapy can have severe or even fatal complications, such as an inflammatory response called cytokine release syndrome, notes Maloney. Thus, T-cell infusions should take place in high-volume centers where experienced providers can handle any complications.

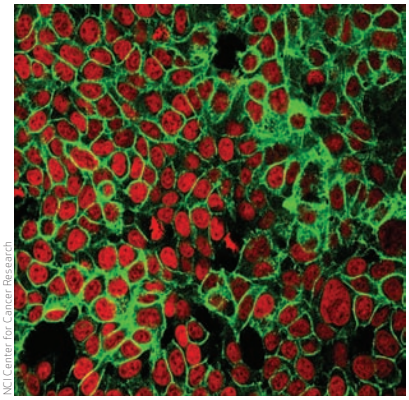
Although challenges remain, the expected approval of tisagenlecleucel represents a complete shift in oncologists' ability to treat advanced leukemia and is likely to be used broadly in patients with advanced disease, Maloney says.

"The hope is that this will be a one-time curative therapy for many patients," he says. "While we still need to understand why some patients relapse, this is a treatment that's proven to be effective in patients when nothing else has worked." –*Janet Colwell* ■

Spreading Colon Cancer Can Bypass Lymph Nodes

When colon cancer spreads, malignant cells often travel directly to the organs, skipping the lymph nodes, a new evolutionary analysis suggests (Science 2017;357:5560).

More than 150 years ago, scientists noticed that metastases often appeared in the lymph nodes before they did in distant organs. That observation suggested that metastatic cells colonized the lymph nodes first. Node removal has long been a standard surgical procedure to prevent metastasis and to stage cancers, but some studies have questioned whether the practice improves survival, and the issue remains contentious.



NCI Center for Cancer Research

Researchers have found that metastasizing colon cancer cells (above) do not necessarily pass through lymph nodes.

To determine the metastatic route for colorectal cancer cells, Kamila Naxerova, PhD, of Massachusetts General Hospital in Boston, and colleagues obtained archived biopsy samples from 17 patients with the disease. The researchers then analyzed 20 to 43 noncoding regions that contain long, uninterrupted stretches of the nucleotide base guanine. These regions don't influence a cancer cell's ability to metastasize, but their rapid mutation rate enabled the researchers to construct evolutionary trees for the primary tumors, distant metastases, and lymph node metastases.

The researchers found that 35% of the time, distant metastases were evolutionarily closer to lymphatic metastases than to the primary tumor, suggesting that the metastases descended from lymph node deposits. But 65% of the time, the distant and lymph node metastases appeared to have arisen from distinct subclones within the primary tumor, which supports the idea that the lymph nodes did not serve as a way station for the metastasizing cells. "In most cases, lymph nodes are not essential intermediaries, at least for colorectal cancer," says Naxerova.

"It's a very nice way of showing what is true and what isn't true in our understanding of how cancer is spread," says Sanford Markowitz, MD, PhD, of Case Western Reserve University in Cleveland, OH. Markowitz notes that after *Science* published the findings and a commentary he wrote about them, a number of posts on social media claimed that the study showed that removal of lymph nodes was no longer necessary (Science 2017;357:35–6). He disagrees, emphasizing that the results "do not mean that lymph nodes cannot be a source of disseminated disease."

S. David Nathanson, MD, of the Henry Ford Health System in Detroit, MI, says that the trend for the last 20 years has been to remove fewer lymph nodes, "so I don't think that this [paper] will change much in terms of clinical practice."

Colorectal cancer may not be a typical solid tumor when it comes to metastasis, says Hellmut Augustin, PhD, of Heidelberg University and the German Cancer Research Center, also in Heidelberg, because cancer cells can metastasize to the liver through the portal vein without involvement of the lymphatic system or the general circulation. "The issue clinically is whether this is relevant for tumors like breast cancer and melanoma," where surgeons have to decide whether to perform surgery on the primary tumor with or without lymph node removal.

Naxerova says that the analysis probably wouldn't work for breast cancers, in which the guanine-containing regions accumulate mutations too slowly to provide an evolutionary signal. However, the technique might illuminate the origins of metastases in cancers where the regions change more rapidly, including melanoma and renal, gastric, and pancreatic cancers. *–Mitch Leslie* ■

Biomarker for Antitumor Immunity Identified

Investigators have discovered that the presence of a certain type of immune cell in tumors may be a biomarker of response to immunotherapy. The findings may help oncologists predict which patients are most likely to benefit from checkpoint inhibitors and potentially aid in developing more effective cancer vaccines.

The researchers analyzed immune cells in the tumors of patients with lung cancer who hadn't yet been treated and found an association between better outcomes and higher density of a subpopulation of tumor-fighting CD8 T cells known as tissue-resident memory (TRM) cells. The finding may explain, in part, why many patients do not respond to immunotherapy regardless of the density of CD8 T cells in their tumors (Nat Immunol 2017;18:940–50).

"When we looked at the T-cell gene expression profile of tumors with good versus bad outcomes, one thing that stood out was the TRM signature," says study co-author Pandurangan Vijayanand, MD, PhD, associate professor at the La Jolla Institute for Allergy & Immunology in California. "Having a high number of TRM cells in their tumors tends to put patients at a very low risk of dying or having recurrence."

TRM cells are already known to play a critical role in fighting infection in the lungs and are known to play an important role in promoting the effectiveness of influenza vaccines, notes Jonathan Powell, MD, PhD, professor of oncology at Johns Hopkins Medicine and associate director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy in Baltimore, MD. However, before this study very little was known about their role in cancer.

"It was surprising to learn that TRM cells in tumors represent a powerful marker for a positive prognosis," he says. "These findings have the potential to help us predict which patients will respond to checkpoint blockade. They also suggest that efforts to develop new vaccines should be focused on generating these types of antitumor cells."

The results also suggest that analyzing the composition of T cells in patients' tumors should become a routine part of clinical trials and cancer treatment, says Vijayanand. Transcriptional profiling of patients' immune cells both pre- and post-treatment could provide a rationale for selecting appropriate immunotherapies and assessing patients' responses as treatment progresses.

The strategy used in this study—purifying relevant immune-cell populations from relatively small tissue samples and performing RNA sequencing to generate genome-wide transcriptional data—can be applied to any accessible tumor type, notes Vijayanand. The approach could become a standard method of identifying biomarkers of response to immunotherapy and aid in discovering novel drug targets.

"In addition to sending tumor tissue for genome sequencing or standard