PEOPLE

Julie M. Vose, MD, MBA, an internationally recognized expert in the treatment of lymphoma and chief of the Oncology/Hematology Division at the University of Nebraska Medical Center in Omaha, began a 1-year term as president of the American Society of Clinical Oncology (ASCO) at its 2015 Annual Meeting in Chicago, IL, on June 1. Since 2006, she has served as the associate director of clinical research and co-chair of the lymphoma program at the institution's Fred and Pamela Buffet Cancer Center.

Johns Hopkins University

Suzanne L. Topalian, MD, professor of surgery and oncology and director of the melanoma program at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine in Baltimore, MD, received the Karnofsky Memorial Award on May 30 at the ASCO meeting. The award recognizes her outstanding contributions to cancer research, diagnosis, and treatment. Her studies of human antitumor immunity have provided a foundation for the translational development of cancer vaccines, adoptive T-cell transfer, and immunomodulatory monoclonal antibodies.

F. Carter Smith

Also at the ASCO meeting, **James P. Allison, PhD,** professor and chair of The University of Texas MD Anderson Cancer Center Department of Immunology in Houston, received the Science of Oncology Award on May 31. The award salutes his groundbreaking studies on T-cell response mechanisms and the application of that knowledge to overcome cancer's ability to evade the immune system. His discoveries led to the clinical development of ipilimumab (Yervoy; Bristol-Myers Squibb) to block CTLA-4.

Expanding the Reach of Anti–PD-1 Therapy

Therapies that expose tumors to immune surveillance by preventing interactions between the PD-1 receptor and its ligands, PD-L1 and PD-L2, continue to generate excitement in the oncology field, with pembrolizumab (Keytruda; Merck) and nivolumab (Opdivo; Bristol-Myers Squibb)—both approved for metastatic melanoma, and the latter for advanced squamous non–small cell lung cancer (NSCLC)—now being evaluated in other solid tumors.

At the American Society of Clinical Oncology's Annual Meeting in Chicago, IL, May 29–June 2, results from investigations of pembrolizumab in metastatic head and neck squamous cell carcinoma (HNSCC), and nivolumab in advanced liver cancer and non-squamous NSCLC, were reported. "These common cancers have been quite refractory to treatment and not previously considered candidates for immunotherapy," said Lynn Schuchter, MD, chief of hematology and oncology at the University of Pennsylvania School of Medicine.

In the KEYNOTE-012 study, the objective response rate (ORR) to pembrolizumab among 132 patients with HNSCC was 24.8%, with half responding within 9 weeks; 86% of responses are ongoing. Drug activity was independent of PD-L1 status and occurred among patients whose disease was positive for human papillomavirus (HPV; primarily nonsmokers) or negative for HPV (mostly smokers).

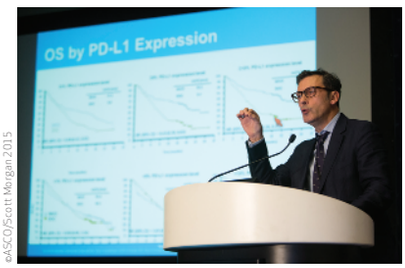
"Pembrolizumab is twice as good as our only approved targeted therapy, cetuximab [Erbitux; Bristol-Myers Squibb]," said the study's lead author Tanguy Seiwert, MD, assistant professor of medicine at the University of Chicago. Just 13% of patients respond to cetuximab, and recent data suggest it is less effective in HPV-positive tumors. Pembrolizumab was well tolerated, with the main side effects being fatigue and hypothyroidism.

Nivolumab was evaluated in a phase I/II study for advanced liver cancer, and 19% of 42 evaluable patients responded. "To put this in context, the response rate with our only approved systemic therapy, sorafenib [Nexavar; Onyx Pharmaceuticals], is just 2%," said the study's lead author Anthony El-Khoueiry, MD, director of the phase I program at the University of Southern California's Norris Comprehensive Cancer Center in Los Angeles. "Two patients' tumors completely disappeared, and six of the eight responses are ongoing, highlighting the durability of this immunotherapy."

Nivolumab was active and well tolerated even in patients with hepatitis B or C infections. The main side effects were elevated amylase and lipase levels along with abnormal liver enzymes, all unaccompanied by clinical symptoms. "Importantly, the 1-year overall survival [OS] rate was 62%, compared to 30% with sorafenib," El-Khoueiry noted. "We'll need to verify our findings in larger studies, but immunotherapy may have a role in treating liver cancer."

Meanwhile, in the phase III CheckMate 057 study, nivolumab extended the OS of patients with advanced non-squamous NSCLC by 3 months, compared with standard docetaxel. In this study, 582 patients were randomized, independent of PD-L1 status, to receive either drug. The ORRs with nivolumab and docetaxel were 19% and 12%, respectively; the median duration of response was significantly longer with nivolumab—17.2 months, compared with 5.6 months with docetaxel. Nivolumab had a favorable safety profile: 10% of patients experienced moderate to severe side effects, versus 54% of those given docetaxel.

"In our study, PD-L1 expression emerged as a predictive factor for benefiting from nivolumab," noted the study's lead author Luis Paz-Ares, MD, PhD, a professor of medicine at Hospital Universitario 12 de Octubre in Madrid, Spain: The median OS for patients expressing PD-L1 in 1% or more of their tumor cells was 17.2 months with this immunotherapy, versus 9.0 months with docetaxel; this 8-month difference doubled for patients with higher (>5%) PD-L1 expression. Paz-Ares called this a "huge magnitude of benefit," adding that "there were no survival differences between nivolumab and docetaxel for



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Luis Paz-Ares, MD, PhD, presents the results of a phase III study comparing nivolumab and standard docetaxel in non-squamous non-small cell lung cancer.

patients with low [<1%] or undetectable PD-L1 expression."

For both pembrolizumab and nivolumab, however, PD-L1 expression is not yet a definitive biomarker; additionally, "we still need the right 'negative' biomarker that says you shouldn't be given [anti–PD-1] therapy, because you won't benefit," Paz-Ares said.

"Developing resistance to single forms of immunotherapy is likely inevitable," El-Khoueiry added. "The future is about finding different ways to stimulate the immune system at the same time, to maximize its impact on tumors." ■

NCI Prepares to Launch MATCH Trial

The NCI will soon launch the NCI-Molecular Analysis for Therapy Choice (MATCH) trial, a multi-armed drug trial that assigns patients with various advanced solid tumors and lymphomas to phase II studies based on genetic alterations in their tumors. NCI-MATCH and other so-called basket trials may eventually lead to cancer drug approvals based on a tumor's genomic profile rather than its tissue of origin.

The announcement was made on June 1 at the American Society of Clinical Oncology's annual meeting in Chicago, IL.

When the trial starts this month, NCI-MATCH investigators will use next-generation sequencing to analyze tumor biopsies from approximately 3,000 adults to identify 143 genetic mutations targeted by drugs approved for other indications or those that have shown efficacy in late-stage clinical trials. About 1,000 patients with actionable mutations—up to 25% of them associated with rare cancers—will then be enrolled in a treatment arm based on their genetic abnormality.

Considered a basket study because it groups patients into parallel cohorts based on mutation status instead of cancer type, NCI-MATCH will take place at 2,400 sites affiliated with the NCI's National Clinical Trials Network and Community Oncology Research Program as well as the ECOG-ACRIN Cancer Research Group, which is leading the study. A similar pediatric trial is under development by the NCI-funded Children's Oncology Group for children with advanced cancers that have progressed on standard therapy.

NCI-MATCH will start with 10 arms, each enrolling up to 35 patients; the number of experimental arms could increase to 25 or 30 within a year, says principal investigator Keith Flaherty, MD, director of clinical research and the Termeer Center for Targeted Therapies at Massachusetts General Hospital Cancer Center in Boston. The trial uses a master protocol, which allows investigators to run concurrent studies under one overarching protocol and to add or terminate arms based on patients' responses. Patients with more than one actionable mutation may switch arms if they do not respond to their initial therapy.

"This trial is a way of fleshing out how broadly effective a drug might be," says Flaherty. "We know that certain drugs that target specific mutations are useful in a handful of cancer types, but we know very little about how these various targeted drugs work in other types of cancer with the same mutation."

The primary and secondary endpoints for the trial will be overall response rate (ORR) and 6-month progression-free survival (PFS), respectively. Investigators will look for an ORR of at least 16% to 25% and 6-month PFS of at least 35% as indications that a particular drug or drug combination may merit further study.

The FDA will consider approving drugs for specific cancers based on phase II evidence, especially if the drug has already been approved for another cancer with the same mutation, says Flaherty. In cases where an unapproved drug shows effectiveness—judged by a response rate of 50% or higher in a targeted population—investigators might launch a larger, confirmatory trial to validate the findings before seeking approval.

A targeted therapy can have a profound impact on one type of tumor but little effect on another with the same genetic mutation, says Barbara Conley, MD, associate director of the Cancer Diagnosis Program at the NCI's Division of Cancer Treatment and Diagnosis. For example, the BRAF inhibitor vemurafenib (Zelboraf; Genentech), approved for patients with BRAF-mutant melanoma, is ineffective against BRAF-mutant colorectal tumors.

One goal of NCI-MATCH, she says, is to identify the features of various tumor types with the same mutation that cause them to either respond to or resist treatment with a targeted therapy. The data may eventually lead to earlier, more effective treatments.

"As our databases grow larger, we may be able to transition from treating patients at the end of their clinical journey to treating them up front, as soon as they present with a malignancy," says Jeff Boyd, PhD, the senior vice president of molecular medicine at Fox Chase Cancer Center in Philadelphia, PA. "The ultimate goal is to get these targeted drugs to cancer patients earlier in the process and to realize improvements in overall survival." ■

Devices Test Drugs in Patients' Tumors

Because people with the same cancer can respond differently to the same therapy, it's important to "identify the best therapy and kill the tumor effectively the first time around," says biophysicist Oliver Jonas, PhD, a postdoctoral fellow working with Robert Langer, ScD, at Massachusetts Institute of Technology (MIT) in Cambridge.

The best way to gauge a drug's effectiveness is to study it in a tumor's natural environment—inside the patient, says Richard Klinghoffer, PhD, chief scientific officer at Presage Biosciences in Seattle, WA. Cell cultures and animal models don't reproduce key features of the tumor's microenvironment.

Jonas and Klinghoffer are the lead authors of two studies describing experimental devices designed to simultaneously test multiple cancer drugs directly in the patient. Their work was recently published in *Science Translational Medicine*.