development and treatment for lung cancers, according to a recent study.

In the study, investigators at 14 U.S. hospitals participating in the Lung Cancer Mutation Consortium tested the tumors of 1,007 patients with metastatic lung adenocarcinomas for at least one driver mutation; 733 patients had their tumors fully genotyped and were tested for 10 driver mutations (JAMA 2014;311:1998–2006). Of the latter group, 64% had actionable drivers, and in 28% of those cases, physicians matched the patients to existing targeted therapies or clinical trials.

Although patients in the study with oncogenic drivers who received targeted therapy lived about a year longer than other patients, randomized trials would be needed to prove a causal link, says Mark G. Kris, MD, a thoracic oncologist at Memorial Sloan Kettering Cancer Center in New York, NY, and co–lead investigator of the study. The significance of this study lies in proving that it's possible to look for multiple targets in a single tumor specimen at diagnosis and use those findings to select individualized therapies.

"This wasn't just a theoretical experiment," says Kris. "We tested the tumor tissue of current patients and the results were sent to their physicians to aid in their care."

The 10 drivers were selected based on a reported frequency of at least 1% in lung adenocarcinomas and the availability of targeted drugs—either approved or under development—when the trial began in 2009. Among the tumors that were evaluated for all 10 drivers, the most common drivers were KRAS (25%), EGFR (21%), and ALK (8%).

When the trial began, the only targeted drugs approved to treat lung cancers were EGFR inhibitors. However, the study helped in the development of other therapies, says Kris, by assigning patients to clinical trials of the ALK inhibitor crizotinib (Xalkori; Pfizer), which received accelerated approval in 2011, and the BRAF inhibitor dabrafenib (Tafinlar; GSK), which earned Breakthrough Therapy designation early this year.

"Clearly, these findings demonstrate the feasibility of prospectively incorporating genomic testing into clinical trial designs and, if effective, into clinical care," write Boris Pasche, MD, PhD, and Stefan Grant, MD, JD, MBA, in an accompanying editorial (JAMA 2014;311:1975–6). "The study also highlights the need for a fundamental shift in how clinical trials are conducted in patients with lung cancers and, by extension, in an increasing number of other malignancies in which oncogenic drivers can be targeted."

The FDA's approval late last year of the first next-generation genomic sequencer, Illumina's MiSeqDx, gave researchers and clinicians an even more powerful tool to search for genetic changes, Kris adds.

"By switching to next-generation platforms, we're able to test for hundreds of genes instead of just 10," he says. "We're finding both unexpected genetic alterations that have targeted therapies available as well as new targets that will be researched to see how relevant they are to lung cancers and whether new therapies could be designed for them."

The study also serves as a model for collaboration among government funders, researchers, and industry, says Kris.

"The study was funded by the National Cancer Institute but the trials were paid for by pharmaceutical companies," he says. "It's a great example of using federal dollars as seed money and the resources of the pharmaceutical industry to act upon the targets our research found." ■

MK-3475 Effective Against Melanoma

Immunotherapy is now a byword in cancer treatment, and current pursuits include designing antibodies against the immune system's "negative" checkpoint proteins. Consider ipilimumab (Yervoy; Bristol-Myers Squibb), which binds to and blocks CTLA-4, unleashing an antitumor response led by cytotoxic T cells that CTLA-4 would otherwise hold at bay.

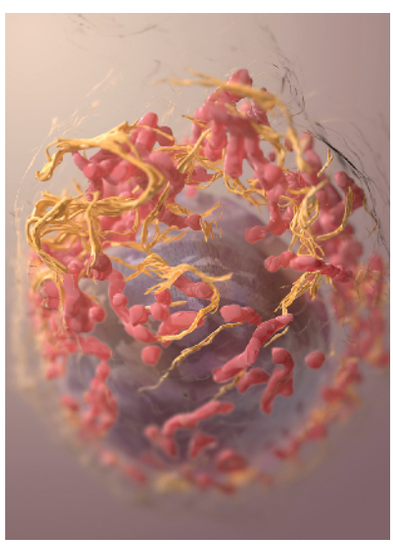
In 2011, ipilimumab became the first immune checkpoint inhibitor approved by the FDA for melanoma. A series of other investigational drugs such as pembrolizumab (MK-3475; Merck) have since sparked further excitement in the immunotherapy field. Pembrolizumab targets a different "negative" immune checkpoint protein called PD-1.

Researchers reported in June that pembrolizumab produces long-term responses in patients with advanced melanoma. Results from the large phase I study of 411 patients were presented at the American Society of Clinical Oncology's Annual Meeting in Chicago, IL.

"Cancer cells use the PD-1 pathway as a signal saying, 'Don't kill me, immune system,'" said principal investigator Antoni Ribas, MD, PhD, director of the tumor immunology program at the Jonsson Comprehensive Cancer Center of the University of California, Los Angeles. "By blocking PD-1 and preventing its ligands PD-L1 and PD-L2 from binding, pembrolizumab releases the brakes on T cells so they can attack the tumor."

Initiated in December 2011, the study encompassed three single-agent dosing strategies and seven cohorts that included patients with and without previous ipilimumab treatment. Overall, 34% of patients met the RECIST objective response criteria. As of October 2013, 88% had sustained their objective responses.

The median overall survival has not been reached, with 1-year survival estimated at 69%. The median progression-free survival was 5.5 months.



Sriram Subramaniam, NCI

3D structure of a melanoma cell derived by ion abrasion scanning electron microscopy. The FDA is expected to decide whether to approve the therapy pembrolizumab (MK-3475) for the disease by the end of October.

Fatigue, pruritus, and rash were the most common adverse events.

Steven O'Day, MD, an immunologist at the University of Southern California's Keck School of Medicine in Los Angeles, called pembrolizumab's mild toxicity profile "almost unheard of in metastatic cancer."

Earlier this year, two phase I studies in pembrolizumab-treated advanced melanoma and non–small cell lung cancer (NSCLC) patients found PD-L1 is potentially a predictive biomarker for drug response.

In melanoma, the overall response rate was 46% when tumors expressed PD-L1 compared to 17% when tumors had no PD-L1. In NSCLC, the response rates to pembrolizumab were 37% in patients whose tumors had high pretreatment levels of PD-L1 versus 11% in those with low pretreatment levels. The findings were presented at the American Association for Cancer Research's 2014 Annual Meeting in April.

The FDA has granted priority review to pembrolizumab for advanced melanoma, with a decision anticipated by October 28.

O'Day hailed pembrolizumab as infinitely preferable to the "high collateral damage" of cytokine therapy for melanoma. "This is truly a brave new world for immunotherapy," he said. "The revolution is here, and it's bursting out of melanoma into other solid tumors." ■

Blocking CD47 Shrinks Pancreatic Tumors

In a new study, blocking CD47, which was found at elevated levels on the surface of pancreatic cancer cells, caused tumors to shrink in preclinical models, suggesting a potential therapeutic strategy for patients with the disease. The research was presented at the American Association for Cancer Research special conference, Pancreatic Cancer: Innovations in Research and Treatment, held May 18–21 in New Orleans, LA.

Researchers in the laboratory of Irving L. Weissman, MD, director of the Institute for Stem Cell Biology and Regenerative Medicine and the Ludwig Center for Cancer Stem Cell Research, both at Stanford University School of Medicine, Stanford, CA, obtained tumor samples from 39 patients with pancreatic neuroendocrine tumors and from 39 patients with pancreatic ductal adenocarcinoma who had surgery to remove their tumors. They found that CD47 was expressed at elevated levels on the surface of cells from both types of tumors and on tumor-initiating cells, which propagate disease and cause metastasis.

"CD47 is a widely expressed cell-surface protein that functions as a 'don't eat-me' signal," explained Geoffrey W. Krampitz, MD, who presented the team's work. "It binds to its receptor, SIRPα, [found] on macrophages and dendritic cells, inhibiting [the cancer cells'] ability to phagocytose." As a result, the cancer can continue to grow and spread.

The researchers tested the effects of blocking CD47 in multiple preclinical models of both pancreatic neuroendocrine tumors and pancreatic ductal adenocarcinomas using the monoclonal antibody Hu5F9. In one model, tumors from patients with the diseases were implanted into mice that were subsequently treated with Hu5F9. Krampitz said that the tumors were eliminated and that the animals experienced fewer metastases and lived longer than controls.

"Furthermore, we have shown that blocking CD47 with monoclonal antibodies and other agents can dramatically enhance the efficacy of cancer-targeting immunotherapies, including rituximab [Rituxan] for lymphoma and trastuzumab [Herceptin] for breast cancer," noted Krampitz. "In addition, we have shown that anti-CD47 antibody treatment selectively increases the ability of macrophages to prime and activate cytotoxic T lymphocytes, which may limit tumor growth beyond the time of anti-CD47 monoclonal antibody treatment."

Based on their preclinical data, Krampitz said that later this year his team will begin to examine the safety profile of Hu5F9, which is also under investigation in hematologic malignancies, in patients with pancreatic cancer. ■

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.

NOTED

- **The FDA reclassified sunlamp products and UV lamps intended for use in these products from low-risk to moderate-risk devices, which will subject them to greater regulation,** such as the need to obtain FDA clearance before marketing them. In addition, sunlamp products must now carry a visible black-box warning that explicitly states that they should not be used on people under age 18.
- **Private insurers and Medicare should pay for proton beam therapy for ocular melanoma, certain brain tumors, and other relatively uncommon cancers** for which the treatment has proven effective, according to a "model policy" issued by the American Society for Radiation Oncology and available at www.astro.org.
- **Asymptomatic, nonpregnant adults and adolescents at high risk of hepatitis B virus (HBV) infection should be screened for it,** according to a recommendation from the U.S. Preventive Services Task Force, which reviewed evidence of potential risks and benefits of screening (Arch Intern Med 2014;161:58–66). The recommendation is a reversal of the task force's 2004 position on HBV screening. About 15% to 25% of people with chronic HBV infection die of cirrhosis or hepatocellular carcinoma.
- **Myriad Genetics (Salt Lake City, UT) sued Pathway Genomics (San Diego, CA) for infringement of its patent claims on *BRCA1* and *BRCA2* genetic testing.** The suit was spurred by Pathway's launch in June of a next-generation sequencing test called *BRCA*True that assesses alterations in the two genes.
- The Centers for Disease Control and Prevention reported that **cigarette smoking rates among high school students have dropped to the lowest levels since the National Youth Risk Behavior Survey began in 1991.** According to the 2013 survey results, the teen smoking rate is down to 15.7% (see www.cdc.gov/mmwr/pdf/ss/ss6304.pdf).
- *The Times of India* reported that **the Indian Patent Office denied a patent for Celgene's anticancer drug Abraxane (nab-paclitaxel),** claiming that it lacks "an inventive step." Under Indian law, patents cannot be granted to new forms of known substances unless they show enhanced efficacy over the known substance.