drawn up a new risk-management strategy to help cancer researchers incorporate biomarkers into clinical trials and avoid potential pitfalls.

Five experts from the European Organization for Research and Treatment of Cancer (EORTC), the NCI, and the National Cancer Research Institute in the UK decided to draw up the recommendations because they all were seeing the same problems with biomarker use in clinical trials. "We want to raise key points to the principal investigators who design and conduct the trials," says co-author Jacqueline Hall, PhD, former head of translational research at the EORTC and coordinator of the working group.

The authors advocate a risk-management approach because which biomarkers a clinical trial includes and how they are measured can have an impact on patients' health, the trial's outcome, and even the future usefulness of the biomarkers. For example, relying on a poorly chosen biomarker could mean that some patients receive inadequate treatment. If the biomarker is uncommon, the trial could languish because of the difficulty of recruiting subjects.

The recommendations, which the authors describe in *The Lancet Oncology*, emphasize a step that seems self-evident but that many researchers skimp on: planning (Lancet Oncol 2014;15:e184–93). "The main difficulty generally is that people don't start early enough, and they don't begin with the end in mind," says study co-author Tracy Lively, PhD, deputy associate director of the Cancer Diagnosis Program at the NCI.

Lively and her colleagues advise researchers who design clinical trial protocols to focus on issues like the justification for a particular assay, the qualifications of the lab that will conduct the tests, and the experience of the biobank that will hold the samples. To make good decisions about biomarkers, the authors note, clinical researchers need to consult with other experts, including pathologists and statisticians.

Once the trial has begun, the authors add, researchers need to continue their efforts, monitoring assay performance and sample banking, for instance. Once the trial concludes, they must still deal with issues like access to banked samples.

Although following the recommendations will increase the amount of time and intellectual effort that researchers have to put into planning clinical trials, doing so is as important as setting appropriate drug doses and treatment schedules, says Lively.

Hall adds that she and her co-authors hope the recommendations will be adopted by agencies that review proposed clinical trials and that they'll spur cancer researchers to improve the use of biomarkers. "It's a call to the community to get involved," she says. ■

T-Cell Therapy for Cervical Cancer

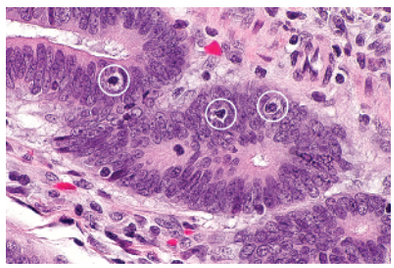
Pitting the immune system against human papillomavirus (HPV) may be a promising strategy for treating women with advanced cervical cancer, according to a small, federally funded phase II study. The results were reported by Christian Hinrichs, MD, an assistant clinical investigator at the NCI in Bethesda, MD, during the American Society of Clinical Oncology's Annual Meeting in Chicago, IL, May 30–June 3.

More than 4,000 women in the United States die from cervical cancer each year. Their median survival is 13 months on chemotherapy and 17 months if bevacizumab (Avastin; Roche) is added.

In this study, researchers used an approach called tumor-infiltrating lymphocyte (TIL) therapy, which has had some success in treating metastatic melanoma and B-cell malignancies. They isolated T cells from patients' tumors and selected those with reactivity with HPV oncoproteins E6 and E7. The TILs were then expanded and infused back into each patient, along with IL2, a T-cell growth factor.

All 9 patients in the study had either HPV-16 or HPV-18 infections, which together cause about 80% of cervical cancers. Two women with widespread metastases and chemotherapy-resistant disease achieved complete and lasting remissions of 11 and 18 months, respectively, at the time of analysis.

"This provides the first proof-of-principle that HPV-targeted TIL therapy can induce regression in cervical cancer," Hinrichs said.



Nephron/CC BY-SA 3.0

Researchers are testing an approach called tumor-infiltrating lymphocyte (TIL) therapy in various cancers, including melanoma, cervical cancer, and colorectal cancer (above). TILs are circled in white.

Hinrichs cautioned that HPV-TIL therapy "is still considered experimental and associated with significant side effects," mainly bone marrow suppression and an increased infection risk due to neutropenia. However, he added, "these toxicities are fully reversible, and it's a one-time treatment."

One challenge associated with personalized immunotherapy is that the antigens targeted by T cells often exist in cells elsewhere in the body, not just in cancer cells. However, the E6 and E7 viral oncoproteins make "extremely attractive targets," said Hinrichs, because they are expressed only in infected tissue.

The study's results are limited but striking. "These are young women who failed multiple attempts at tumor-directed therapy," said Steven O'Day, MD, an immunologist at the University of Southern California's Keck School of Medicine in Los Angeles. "By ignoring the cancer cells and, instead, activating T cells, we've provoked a few durable responses in a disease generally not seen well by the immune system."

Hinrichs is now exploring why this therapy was highly effective in only some women. "The next step, to better clarify the response rate, is to treat more patients—we're expanding to 35," he said. "We've also added a patient cohort with noncervical, HPV-positive cancers to this study." ■

Study Supports Routine Lung Tumor Genotyping

Using multiplex genotyping to identify oncogenic drivers and match patients to individualized therapies has the potential to transform drug

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.

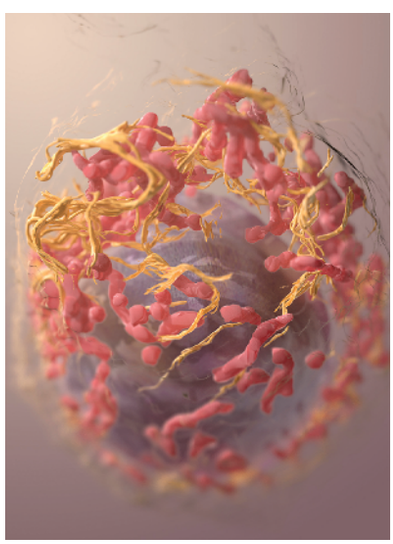
In 2011, ipilimumab became the first immune checkpoint inhibitor approved by the FDA for melanoma. A series of other investigational drugs such as pembrolizumab (MK-3475; Merck) have since sparked further excitement in the immunotherapy field. Pembrolizumab targets a different "negative" immune checkpoint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