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

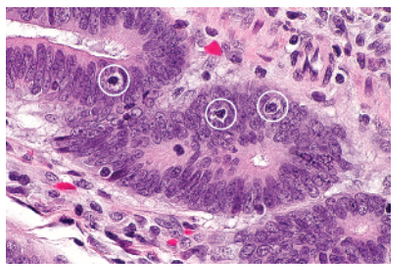
Pitting the immune system against human papillomavirus (HPV) may be a promising strategy for treating women with advanced cervical cancer, according to a small, federally funded phase II study. The results were reported by Christian Hinrichs, MD, an assistant clinical investigator at the NCI in Bethesda, 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.



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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