Robert L. Ferris, MD, PhD, a renowned expert in immunotherapy and a specialist in head and neck cancer, was named director of the University of Pittsburgh Medical Center’s Hillman Cancer Center in Pennsylvania, effective July 1. He succeeds Nancy Davidson, MD, who departed last year. Ferris has worked at the Hillman Cancer Center for the past 15 years, serving as chief of the Division of Head and Neck Oncologic Surgery. He also served as co-leader of the Cancer Immunology Program and was most recently appointed associate director of translational research and co-director of the Tumor Microenvironment Center.

Michael J. Birrer, MD, PhD, a medical oncologist and expert in the early detection and treatment of gynecologic cancers, became director of the University of Alabama at Birmingham Comprehensive Cancer Center on August 1. He succeeds Edward E. Partridge, MD, who retired after serving in that role for the past 10 years. Previously, Birrer was director of medical gynecologic oncology and director of the gynecologic cancer research program at the Massachusetts General Hospital Gillette Cancer Center, led the Dana-Farber/Harvard Cancer Center program in gynecologic cancers, and served as a professor of medicine at Harvard Medical School, all in Boston.

Also this month, Ruben A. Mesa, MD, will begin his new role as director of the UT Health San Antonio Cancer Center. (UT Health San Antonio is the new name of The University of Texas Health Science Center San Antonio.) He replaces Ian M. Thompson, MD, who retired in January. Prior to his move to Texas, Mesa served as chair of the Division of Hematology and Medical Oncology at the Mayo Clinic in Phoenix, Arizona, as well as deputy director of the cancer center there. He is an internationally recognized expert on myeloproliferative neoplasms.

Widespread Genomic Testing Deemed Feasible

Although comprehensive genomic screening has not yet become routine when treating patients with cancer, widespread testing in those with advanced, refractory disease is feasible, according to the ongoing ProfiLER study. The study also found that patients who subsequently received a treatment matched to the genetic changes in their tumor lived longer than those who lacked a so-called actionable mutation.

The findings were presented in early June at the 2017 American Society of Clinical Oncology Annual Meeting in Chicago, IL, by Olivier Trédan, MD, PhD, chair of the Department of Medical Oncology at the Centre Léon Bérard in Lyon, France, and the study’s lead author.

Trédan’s team enrolled 2,676 patients with a variety of cancer types between 2013 and May 2017. DNA extracted from 1,944 tumor samples was analyzed by next-generation sequencing of 69 cancer-related genes and whole-genome array comparative genomic hybridization. At least one actionable alteration, which could be treated with an existing targeted therapy, was found in 52% of patients. The most common actionable mutations were found in the PI3K/mTOR, cyclin, and multitarget tyrosine kinase pathways, and these actionable mutations were detected in many common cancers, including breast; central nervous system; colorectal; gynecologic; head and neck; liver, pancreas, and bilary tract; and lung, as well as sarcomas.

A molecular tumor board recommended a targeted treatment to 676 patients (35% of those tested) based on the availability of drugs that could attack the aberrant protein or pathway. However, just 143 patients (7% of those tested) received the recommended agent, usually as part of a clinical trial. Trédan noted that the other 533 patients did not receive the suggested targeted therapy due to rapid disease progression, not meeting the eligibility criteria for a clinical trial, or difficulties in obtaining the recommended drugs.

Researchers next compared the overall survival rates for patients who received molecularly targeted agents based on genomic testing with 502 patients who did not. After 3 years, 53.7% of patients who received the targeted therapy were alive, compared with 46.1% of those who did not. The 5-year survival rate was also higher—34.8% compared with 28.1%, respectively, Trédan reported.

The researchers “should be applauded for this huge endeavor,” commented Bryan Schneider, MD, of the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis and director of the Indiana University Health Precision Genomics Program.

However, Schneider cautioned that “even though the trends look pretty, the overall survival is not quite statistically significant.” In addition, as with other datasets, he noted that “there is a substantial loss of patients between those who have an actionable mutation and those who get to drug.”

Some trials have had greater success at matching patients to therapy based on their mutational profile. Compared with 7% in the ProfiLER trial, 19% of patients in the just-published MOSCATO 01 trial received targeted therapy (Cancer Discov 2017;7:586–95). In addition, across 10 datasets from several institutions, Schneider noted that as many as 25% of patients received a targeted therapy, with an average of 11%, as in Memorial Sloan Kettering Cancer Center’s IMPACT (Nat Med 2017;23:703–13).

Regardless, “we’ve got to do a better job of getting [patients] to targeted drugs,” Schneider continued. “This clearly mandates broad access to clinical trial options and maybe earlier testing. But importantly, we have to demonstrate where this works, and this will be best learned through our umbrella, basket, and randomized trials.”

Sumanta Kumar Pal, MD, of City of Hope Comprehensive Cancer Center in Duarte, CA, said many patients aren’t yet able to benefit from personalized genomic testing because such screening has not yet become routine in clinical practice.
treatment due to the relative lack of molecularly targeted therapies. In the ProfiLER study, targeted therapies could be recommended for just 35% of the patients whose tumors were analyzed.

However, that number might increase if more genes are tested for aberrations such as point mutations and copy-number variations, Trédan explained. His team plans to launch a randomized clinical trial, dubbed ProfiLER 02, to compare the 69-gene panel used in the clinical trial, dubbed ProfiLER 02, to the current study to a commercial test that analyzes 315 genes. –Suzanne Rose

Dramatic Responses Seen with TRK Inhibitor

The only selective pan-TRK inhibitor currently in clinical development, larotrectinib (LOXO-101; Loxo Oncology), shows striking and lasting efficacy against a variety of tumors—and in both adult and pediatric patients. Data were presented on June 3 at the 2017 American Society of Clinical Oncology Annual Meeting in Chicago, IL.

Researchers reported response data for 50 of 55 patients enrolled in three trials: eight adults from a phase I trial, 12 from the pediatric phase I/II SCOUT trial, and 35 adults and adolescents from the phase II NAVIGATE basket trial. All had advanced, TRK fusion–positive solid tumors, representing 17 different types of cancer; some were rare cancers, such as infantile fibrosarcoma and salivary gland cancer, whereas others, such as melanoma and lung cancer, were common. (TRK fusions occur in about 90% of certain rare cancers, but in only about 0.5% to 1% of common cancers.)

Among the 50 patients who had been on the study long enough to have had at least two scans, 76% responded to larotrectinib. “You’d be hard-pressed to find a targeted therapy, even within a single disease context, that has results like this,” said David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who presented the findings. The median time to response was 1.8 months.

In addition, 12% of patients had complete responses. “These data are early, and there needs to be some equipoise when interpreting them,” said Trever Bivona, MD, PhD, of the University of California, San Francisco. However, he added that the complete response rate “is nearly unheard of” in advanced cancers.

In total, 93% of responding patients remain on therapy—including one ongoing at 25 months—or have had surgery. The five patients who hadn’t been on the study long enough to have a confirmatory scan had an objective response to larotrectinib and remain on the study, Hyman said.

There was no trade-off between improvement and side effects, as larotrectinib was extremely well tolerated, Hyman said, with just 13% of patients requiring a change in dose. No patients discontinued therapy due to adverse events, the most common of which were dizziness, fatigue, and nausea.

In the United States, researchers estimate that 1,500 to 5,000 patients a year are diagnosed with a cancer that harbors a TRK fusion. However, the true number may well be higher because most assays don’t capture TRK fusions.

“You only find what you look for,” said John Heymach, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston. “I think you see very clearly that patients who have this alteration, which is rare, and get this drug, have a dramatic benefit. This speaks to the importance of expanding what we’re looking for.”

Hyman agreed. “Really recognizing this benefit in the community will require that we test patients more universally for TRK fusions or other tumor-agnostic biomarkers such as microsatellite instability,” he commented.

Bivona stressed that cancer researchers also need to look for mechanisms of resistance early in the drug development process. “No matter how effective a targeted therapy is initially, virtually all patients relapse due to resistance and, oftentimes, mutations in the target of the drug,” said Bivona. In the case of larotrectinib, six patients developed resistance to the drug, five of whom had the same mutation.

To address that, researchers tested another agent, LOXO-195, which demonstrated promising activity in two patients who had been treated with larotrectinib (Cancer Discov 2017 June 3 [Epub ahead of print]). These data “highlight the potential value in anticipating those mechanisms of resistance and developing second-generation drugs that target them,” said Bivona.

Loxo Oncology plans to submit an application to the FDA late this year or early in 2018 for the approval of larotrectinib. –Suzanne Rose

Modeling Cancer Mutations in 3-D

Many cancer researchers depend on the Catalogue of Somatic Mutations in Cancer (COSMIC) to quickly identify what is known about a mutation, from its prevalence in different tumor types to the biological pathways it affects (cancer.sanger.ac.uk/cosmic). Now, they can use COSMIC-3D to explore how the mutations in the COSMIC database affect the structure and function of more than 8,000 human proteins (cancer.sanger.ac.uk/cosmic3d).

“With the vast majority of disease-causing mutations identified in coding sequences, we wanted to create a system where these mutations could be easily explored in their structural environments,” says Simon Forbes, PhD, head of COSMIC at the Wellcome Trust Sanger Institute in the UK. Having spent years developing the COSMIC database, his group now seeks to “highlight an enormous range of known and novel targets, to explore novel precision drug design.”
Widespread Genomic Testing Deemed Feasible


Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-NB2017-094

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/7/8/786.2. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.