Dung T. Le, MD, discusses the use of mismatch repair deficiency to predict response to PD-1 blockade in colorectal and other cancers.

patients may not have a mutation that the immune system can recognize," explained Le, adding that researchers plan to further assess the MMR-deficient non-responders.

Although MMR deficiency can occur in many cancer types, including those in the uterus, stomach, biliary tract, pancreas, ovaries, prostate, and small intestine, in addition to colorectal cancer, Le said it is too early to recommend that all patients with cancer be tested for it. Researchers first need to confirm their findings in a larger group of patients. "This was a small study," she said. ■

Study May Yield Breakthrough for DIPG

A recent study suggests that a drug approved for the treatment of multiple myeloma may hold promise for treating diffuse intrinsic pontine glioma (DIPG), a pediatric brain tumor that currently has no effective treatment.

Researchers screened 16 human DIPG cell lines against a panel of 83 promising targeted agents and chemotherapies approved for pediatric brain tumors. The multihistone deacetylase inhibitor panobinostat (Farydak; Novartis) was selected for further study based on its efficacy in 12 of the 16 cell lines.

When the researchers injected the drug into mice implanted with DIPG tumors, they found that it slowed tumor growth. The findings set the stage for a phase I clinical trial of panobinostat, slated to begin by the end of this year (Nat Med 2015;21:555–9).

"This disease is the leading cause of brain tumor death in children, and we've made zero progress in treating it over the past several decades," says the study's senior author Michelle Monje, MD, PhD, a pediatric neuro-oncologist and assistant professor of neurology at Stanford University School of Medicine in Palo Alto, CA. "It's exciting that we have preclinical data that suggests a therapy."

Observing that DIPG cells eventually developed resistance to panobinostat, the researchers also experimented with a combination of panobinostat and GSK-J4 (GlaxoSmithKline), a development-stage demethylase inhibitor that has shown some potential for treating DIPG. They discovered that the two drugs work synergistically to counteract known mechanisms of epigenetic dysfunction in DIPG cells.

Panobinostat's potential as a therapeutic agent is consistent with earlier research showing that about 80% of DIPG tumors harbor recurrent K27M mutations in genes encoding histone H3 that prevent trimethylation, causing broad epigenetic dysregulation, says Monje. By inhibiting histone deacetylase, investigators expected panobinostat to increase acetylation, but they were surprised to discover that it also restored methylation and normalized gene expression.

DIPG has been difficult to study because tumors are enmeshed in the brain stem, cannot be removed, and are not typically biopsied. However, 5 years ago, Monje established the first cell culture of DIPG from an autopsy sample. Similar efforts to obtain tumor tissue for research have led to the development of additional DIPG cell cultures in Monje's lab and in several other labs internationally.

"In the past we would take adult glioblastoma tumors and test those cells for targets, but we now understand that the mutations found in DIPG are not the same as those found in adult tumors," says Mark Kieran, MD, PhD, clinical director, Brain Tumor Center, Dana-Farber/Boston Children's Cancer and Blood Disorders Center in Boston, MA, who was not involved with the study. "What makes this study so unique is that it uses the appropriate targeted cells from actual DIPG patients and shows that, *in vitro*, panobinostat can turn off tumor cell proliferation and, *in vivo*, it can cross into the brain and turn off tumor growth."

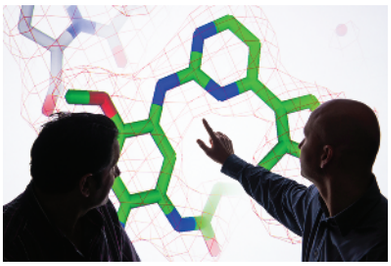
Kieran cautioned that many questions remain about panobinostat's potential in DIPG. For example, while systemic administration of the drug showed effectiveness in mice used in the study, it is not known whether it will cross the blood–brain barrier in children. Monje's team used convection-enhanced delivery to directly infuse panobinostat into the brain stem in mice, but that method has not yet been approved for humans.

"That one drug is suddenly going to knock out DIPG is unlikely, but for a disease where we've seen no progress in 50 years, this paper is an enormous advance in our understanding," says Kieran. "For the first time, we have at least some idea of how to start moving forward." ■

New Options for EGFR-Mutant Lung Cancer

Two new drugs that target the most common cause of acquired resistance to earlier EGFR inhibitors may offer a much-needed treatment option for patients with EGFR-mutated non–small cell lung cancer (NSCLC), according to findings from early-phase clinical trials.

AZD9291 (AstraZeneca) and rociletinib (Clovis Oncology) are third-generation EGFR tyrosine kinase inhibitors that are active against the T790M *EGFR* mutation, the most common mechanism of resistance in patients whose tumors progress after treatment with first-generation EGFR inhibitors, such as erlotinib (Tarceva; OSI Pharmaceuticals) and gefitinib (Iressa; AstraZeneca). In separate trials, AZD9291 and rociletinib were associated with response rates of 61% and 59%, respectively, among T790M-positive patients resistant to first-generation EGFR inhibitors, compared with 21% and 29% among patients without the mutation (N Engl J Med 2015;372:1689–99; N Engl J Med 2015;372:1700–9).



AstraZeneca

Scientists discuss the development of AZD9291, a third-generation EGFR inhibitor.

In both studies, median progression-free survival was significantly higher among patients with the T790M mutation than among those without it: 9.6 months in the AZD9291 trial (253 enrolled patients) and 13.1 months in the rociletinib trial (130 enrolled patients) compared with 2.8 months and 5.6 months, respectively, in patients without the mutation. Both drugs have received Breakthrough Therapy Designation from the FDA and are under evaluation in larger, randomized phase III trials. The manufacturers are expected to file for FDA approval later this year.

The drugs selectively target both the original activating EGFR mutations and the T790M resistance mutation while sparing wild-type EGFR. As a result, patients did not experience the dose-limiting toxic side effects observed with second-generation EGFR inhibitors, such as afatinib (Gilotrif; Boehringer Ingelheim).

"The main toxic effects we were seeing with older drugs were rash and diarrhea, which were caused by the drugs inhibiting wild-type or normal EGFR found in the skin and gut," says the lead investigator of the rociletinib trial, Lecia V. Sequist, MD, clinical researcher at Massachusetts General Hospital Cancer Center in Boston. "These newer drugs avoid wild-type EGFR and are much better tolerated."

The studies emphasize the importance of repeating biopsies in patients with NSCLC at the time of disease progression to test for the presence of the T790M mutation, says Pasi Jänne, MD, PhD, lead investigator of the AZD9291 trial and director of the Lowe Center for Thoracic Oncology at Dana-Farber Cancer Institute in Boston. Currently, there are no approved effective treatment options for T790M-mediated drug resistance.

"With these new drugs we're introducing an alternative that's beneficial, highly active, and well tolerated," he says.

Both studies reported some antitumor activity among patients who tested negative for T790M, which may suggest that T790M is present in some tumor cells at levels too low to be detected in a biopsy, notes Sequist. Her team conducted a follow-up study showing that mutated and wild-type T790 cells can coexist within a single tumor and that both are capable of driving rociletinib resistance.

In that study, researchers examined biopsies from 12 T790M-positive NSCLC patients who experienced progression after treatment with rociletinib, and found that half of the patients tested negative for the mutation at the time of resistance (Cancer Discov 2015 May 1 [Epub ahead of print]). They theorized that rociletinib, while suppressing the growth of T790M-positive cells, may confer a proliferative advantage to a population of T790 wild-type clones within the same tumor, which may mediate the development of resistance.

Jänne co-authored another follow-up study in which researchers identified multiple mechanisms of resistance by analyzing liquid biopsies from some of the patients in the earlier trial whose disease progressed during treatment with AZD9291 (Nat Med 2015;21:560–2).

The findings suggest that combination therapies, using rociletinib or AZD9291 to target T790M and another drug to target wild-type T790, might be effective, Sequist says. Those strategies have been difficult to pursue until now due to the toxicity of earlier-generation drugs.

"Hopefully we can come up with combinations that make real long-term differences," Jänne says. "We're not under the illusion that a single drug can cure advanced lung cancer, but combinations based on biology—and drugs that are tolerable—may ultimately make a long-term difference in patient outcomes." ■

NOTED

- **Pfizer announced the launch of a competitive, peer-reviewed grants program to support clinical research investigating palbociclib** (Ibrance) in advanced breast cancer. The multiyear program will award up to six grants totaling as much as $3 million. For specifics, visit www.aspireresearch.org.
- Under the direction of the National Academy of Sciences and the National Academy of Medicine, **researchers and other experts will convene this fall to explore issues associated with human gene-editing** technologies, such as CRISPR-Cas9, and an international committee will work to recommend standards, guidelines, and practices governing the use of these technologies in biomedical research.
- Roche announced that **the FDA has approved the cobas KRAS Mutation Test for diagnostic use.** The real-time PCR test is designed to identify KRAS mutations in tumor samples from patients with metastatic colorectal cancer and help oncologists determine an appropriate therapy.
- A recent report from the U.S. Centers for Disease Control and Prevention (available at www.cdc.gov) concludes that **about 20% of women are not up to date with cervical cancer screening and 25% are not up to date with breast cancer screening;** about 40% of adults are not up to date with colorectal cancer screening.
- In new guidelines, **the American College of Physicians says that clinicians should screen women ages 21 to 30 who are at average risk of cervical cancer every 3 years,** using the Pap test alone (Ann Inter Med 2015 Apr 30 [Epub ahead of print]). Women younger than 30 should not be tested for human papillomavirus (HPV) as part of cancer screening because of the high prevalence of HPV infection in this age group.
- **Memorial Sloan Kettering Cancer Center announced that it has received a $150 million commitment from David H. Koch.** The contribution will help fund a 23-story, 750,000-square-foot outpatient medical building in New York, NY.

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