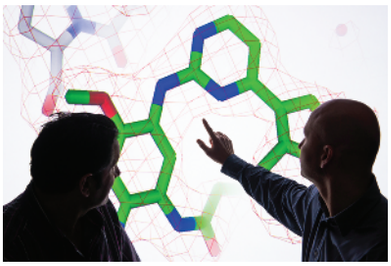

AstraZeneca

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.