The project’s investigators, led by Nikhil Wagle, MD, a medical oncologist at DFIC, aim to create a repository of mineable data to speed breast cancer genomics research, better understand drug resistance, and provide leads for the development of new therapies. To that end, trial participants, all of whom have metastatic disease, agreed to share their medical records with investigators, provide saliva samples for the extraction of germline DNA, and make their tumor tissue available for next-generation sequencing.

Roughly 85% of patients with breast cancer are treated in community settings, where their tissue samples are collected only for initial diagnosis, then stored and not routinely made available for research, Wagle said. Until now, “no one has asked if they’d be willing to share [their samples] with researchers for discovery.”

Joanne Mortimer, MD, director of the women’s cancers program at City of Hope Comprehensive Cancer Center in Duarte, CA, who is not involved in the project, described it as “brilliant.” Patients want to contribute their data so they can better understand their own disease and help others, she said. “Nobody wants to feel like they’ve died in vain.”

To date, most of the project’s participants are white women, Wagle said. He has started additional outreach efforts with advocacy groups to diversify the patient cohort.

“We should be able to reach lots of different people who haven’t been studied using traditional approaches,” he said. Gathering data from patients of different racial and ethnic backgrounds will help fill gaps in knowledge, such as why black women with breast cancer have poorer outcomes than whites.

The power of such patient-driven research, Wagle said, is that it pools data and identifies “rare” patients—for instance, those who carry an uncommon mutation, are younger than typical patients, or have an exceptional response to a particular therapy. These data, which can be challenging for scientists at any one institution to obtain, will be shared (identifying information removed) with the NIH and the broader cancer research community.

“I think that Dr. Wagle has really established a paradigm that we can apply across other cancer types,” said Sumanta Kumar Pal, MD, co-director of the kidney cancer program at City of Hope. “He should be commended for developing a platform that allows for very rapid collection of data.”

-Karen Weintraub ■

New Driver Mutations Detected in NSCLC

A comprehensive genomic analysis of non–small cell lung cancer (NSCLC) has identified additional driver mutations that may guide the development of new targeted drugs and immunotherapy. The findings also highlight key differences between subtypes of NSCLC that could inform future therapeutic management strategies (Nat Genet 2016;48:607–16).

The study researchers profiled two major subtypes of NSCLC via whole-exome sequencing: 660 lung adenocarcinoma (ADC) and 484 lung squamous cell carcinoma (SCC) samples. They found multiple mutated genes along the RAS-RAF signaling pathway that had not been associated with lung ADC, including SOS1, RASA1, and VAV1.

Current targeted therapy research in lung ADC is largely focused on inhibiting receptor tyrosine kinases, including EGFR, that activate RAS-RAF signaling and are often mutated in this disease. The discovery of previously unknown players along a main driver pathway in lung ADC extends the realm of possible therapeutic targets, says senior author Matthew Meyerson, MD, PhD, professor of pathology at Dana-Farber Cancer Institute in Boston, MA. It also underscores the importance of using large sample sizes in genomic studies, he adds. For example, SOS1 was already known to be mutated in patients with Noonan syndrome, a genetic disorder, but previous smaller studies failed to identify it in lung ADCs.

The team also found that 47% of lung ADC and 53% of lung SCC samples had at least five neoepitopes—peptides arising from somatic tumor mutations—that could potentially be targeted by cancer vaccines. The identification of these neoepitopes suggests that in NSCLC, a significant fraction of tumors may respond to immune checkpoint inhibitors, Meyerson observes.

Additionally, he says, this study shows that the two main NSCLC subtypes are more distinct than previously thought. Of 38 mutated genes detected in the lung ADC samples, and 20 detected in lung SCCs, only six were shared by both subtypes. In fact, the mutations and amplifications noted in lung SCC were found to be more similar to other cancers associated with smoking—including head and neck SCC and bladder cancer—than to lung ADC.

“It indicates that there are some very similar pathway abnormalities and mutations that accompany squamous cell tumors, regardless of where they originate,” says Stephen Baylin, MD, co-director of the cancer biology research program at the Sidney Kimmel Comprehensive Cancer Center in Baltimore, MD. “As such, there may be common management strategies that could be used to treat these types of cancer.”

Further research is needed into the role of neoepitopes in immunotherapy, Meyerson notes. “We need to understand the relationship between neoepitopes, especially recurrent ones, and patient responses to immune checkpoint inhibitors,” he says. “Future studies should seek to determine whether predicted cancer neoepitopes are in fact leading to immune responses in lung cancer.”

-Janet Colwell ■

Single-Agent Abemaciclib Active in Breast Cancer

Results from a phase II study indicate that abemaciclib (Eli Lilly), an investigational CDK4/6 inhibitor, demonstrates single-agent activity in women with advanced HER2-negative, ER-positive breast cancer whose disease has progressed on endocrine therapy.
and chemotherapy. The data were presented by Maura Dickler, MD, of the breast medicine service at Memorial Sloan Kettering Cancer Center in New York, NY, during the American Society of Clinical Oncology’s annual meeting in Chicago, IL, June 3–7.

Cell-cycle control is frequently disrupted in ER-positive breast cancer, Dickler said, “making key regulators such as CDK4 and CDK6 rational targets for inhibition” with drugs like abemaciclib, which halts the cell cycle at the G1 phase.

A total of 132 patients with advanced metastatic breast cancer were enrolled on the MONARCH1 study. The objective response rate to abemaciclib was 19.7%, with a median duration of 8.6 months and 28.2% of responses lasting at least 12 months. The median progression-free survival was 6 months, and the median overall survival was 17.7 months.

Abemaciclib was largely well tolerated, especially considering the patient population, Dickler reported: Only 7.6% discontinued treatment due to toxicity, and diarrhea, a main side effect, was quickly resolved. Neutropenia was less commonly seen than with other therapies in this class, “probably because of the drug’s differential impact on CDK6 inhibition,” she said, noting that abemaciclib is 14 times more potent against CDK4 than CDK6.

To date, palbociclib (Ibrance; Pfizer) is the sole CDK4/6 inhibitor to have gained the FDA’s conditional approval as first-line therapy, in combination with letrozole, for postmenopausal women with locally advanced or metastatic HER2-negative, ER-positive breast cancer. Ribociclib (Novartis) is in phase III development; meanwhile, abemaciclib was designated as a Breakthrough Therapy by the FDA in October 2015.

In a study of patients with heavily pretreated, advanced metastatic breast cancer, “any responses we see, we can fairly well assume to be a consequence of the drug,” said Tatiana Prowell, MD, breast cancer scientific liaison with the FDA’s Office of Hematology and Oncology Products. “That’s why most successful Breakthrough Therapy requests, including the one for abemaciclib, have relied on objective and/or durable responses, because the strong sex-effect group, comprised eight cancers—including lung adenocarcinoma and head and neck squamous cell carcinoma (HNSCC)—with unequal male-to-female incidence and mortality ratios. Five cancers, including glioblastoma multiforme and acute myeloid leukemia, were in the weak sex-effect group, which had more balanced incidence and mortality ratios.

The researchers uncovered a variety of sex-biased somatic mutations and copy-number changes in cancers in the strong sex-effect group. For example, men with lung adenocarcinoma had a higher frequency of STK11 mutations: This kinase activates the AMPK pathway, and mutations in its gene are thought to predict sensitivity to the mitochondrial inhibitor phenformin, at least in mouse models of lung adenocarcinoma. Meanwhile, PIK3CA was amplified more often in women with clear-cell renal cell carcinoma, potentially influencing sensitivity to mTOR inhibition; in the same cancer in men, PDCD1, which encodes the immune checkpoint protein PD-1, was more frequently deleted.

The team then scrutinized 114 clinically actionable genes, including 86 whose alterations are targeted by FDA-approved drugs. They reported that 53% showed sex-biased differences in mRNA and protein expression, among other molecular signatures; these 60 genes were almost all found in cancers of the strong sex-effect group. For instance, women with HNSCC had higher levels of sex-biased somatic mutations and protein expression, among other findings: This kinase activates the AMPK pathway, and mutations in its gene are thought to predict sensitivity to the mitochondrial inhibitor phenformin, at least in mouse models of lung adenocarcinoma. Meanwhile, PIK3CA was amplified more often in women with clear-cell renal cell carcinoma, potentially influencing sensitivity to mTOR inhibition; in the same cancer in men, PDCD1, which encodes the immune checkpoint protein PD-1, was more frequently deleted.

The next steps for Liang’s team include validating the sex-biased
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