assessed in NSCLC, often sequentially, which strains tissue availability."

John Carpten, PhD, who heads the Institute of Translational Genomics at the University of Southern California in Los Angeles, agreed. "We've now seen that noninvasive approaches are feasible," he said, "not only to detect and monitor cancer, but also to tailor its clinical management."

The field of circulating biomarkers is one that's growing rapidly, Carpten added, with "new methods with which we can characterize exosomes, for instance, or measure epigenetic changes in cfDNA. Integrating these different tools should allow us to do a much better job in precision oncology." *–Alissa Poh* ■

Combo Drug Strategy Tested for PDAC

Dual inhibition of the cell's recycling process and the KRAS pathway may help salvage two drug strategies that have each failed to work as monotherapies for pancreatic cancer.

Two research teams independently reported that concurrent treatment with an inhibitor of MEK or ERK—two nodes in the KRAS-mediated MAPK cascade—and a form of chloroquine could stunt cancer growth in human cells and in mouse models of pancreatic ductal adenocarcinoma (PDAC). An antimalarial drug, chloroquine targets lysosomes to indirectly block the last stage of autophagy.

"This is an important therapeutic strategy," says Channing Der, PhD, of the University of North Carolina at Chapel Hill, who led one of the studies (Nat Med 2019;25:628–40). "Not only was the combination synergistic," he notes, "but it resulted in cell death."

The discovery that PDAC is typically driven by the oncoprotein KRAS and also by autophagy, a metabolic process that enables the cell to recycle its own parts for energy, led clinicians to evaluate the potential of drugs targeted at both of these pathways. As monotherapies, however, neither approach offered much clinical benefit to patients.

That lack of response can now be explained by the observation that tumors compensate for inhibition of MAPK signaling by ramping up autophagic activity. "It was absolutely night and day: No matter where we blocked the MAPK pathway in various different pancreatic cancer cell lines, we saw this striking upregulation of autophagy," says Martin McMahon, PhD, of the University of Utah in Salt Lake City, who led the other study (Nat Med 2019;25:620–7).

Der and his colleagues showed that disrupting MAPK signaling suppresses glycolysis and mitochondrial function, and that autophagy serves as a backup source of energy. Adding an autophagy inhibitor, such as chloroquine or hydroxychloroquine, to the mix choked off this adaptive response.

Each team studied xenograft PDAC models, treating the mice with the MEK inhibitor trametinib (Mekinist; Novartis) or the ERK inhibitor SCH772984 (Merck) plus chloroquine or hydroxychloroquine. This dual therapy more effectively blunted tumor progression and extended survival than either agent alone.

"All the mechanistic data is there for a rational approach to combine these drugs in the clinic," says Nabeel Bardeesy, PhD, of the Massachusetts General Hospital Cancer Center in Boston, MA, who was not involved in either study.

McMahon's colleague Conan Kinsey, MD, PhD, has already begun testing the strategy in patients. Prompted by the laboratory data, last year Kinsey administered trametinib plus hydroxychloroquine on a compassionate-use basis to a 68-year-old patient who was refractory to standard therapies and likely had only about a month to live.

The treatment shrank the man's tumor burden by about 50%. He died about 7 months after treatment, but his partial response inspired Kinsey to launch a phase I trial to further evaluate the combination strategy with increasing doses of hydroxychloroquine. That study has enrolled three patients so far, with no dose-limiting toxicities.

Meanwhile, Der's team is working with another group to initiate a similar clinical trial for patients with PDAC to test the MEK inhibitor binimetinib (Mektovi; Array BioPharma) plus hydroxychloroquine. *–Elie Dolgin* ■

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NOTED

Norman E. "Ned" Sharpless, MD, became acting commissioner of the FDA in April, replacing Scott Gottlieb, MD, who resigned. Sharpless had served as the NCI's director since October 2017. Deputy NCI Director Doug Lowy, MD, will become the NCI's acting director. Gottlieb was confirmed as head of the FDA in May 2017.

The FDA granted accelerated approval to atezolizumab (Tecentriq; Genentech) in combination with nab-paclitaxel (Abraxane; Celgene) for patients with inoperable advanced or metastatic triple-negative breast cancer whose tumors express PD-L1. In a phase III trial, the combination extended median overall survival by 2.6 months compared with a placebo plus nab-paclitaxel. A PD-L1 inhibitor, atezolizumab is the first immunotherapy approved for breast cancer.

Researchers developed an ALK-targeted antibody–drug conjugate for neuroblastoma (Science Transl Med 2019;11:eaau9732). The drug, CDX-0125-TEI, combines a monoclonal antibody that recognizes ALK-expressing cells with the alkylating chemotherapy agent thienoindole. In laboratory experiments, it eliminated neuroblastoma cells in mouse models and cell cultures without damaging healthy cells.

The FDA granted breakthrough designation to an artificial intelligence (AI) tool designed by Paige.AI, the first such technology to receive the designation for cancer diagnosis. Launched last year, the company is training its deep-learning AI tool on digitized cancer pathology slides—to date, the company has more than 1 million slides, with another 4 million to be added across cancer subtypes. Paige.AI plans to first market its AI technology for prostate cancer.

Medicaid coverage of lung cancer screening for high-risk individuals varies widely by state, according to an American Lung Association report (available at https://www.lung.org). The report notes that 31 states cover screening through Medicaid and 12 states do not; seven others do not have publicly available policies. In total, 26.3% of those on Medicaid are current smokers, a key risk factor for developing lung cancer.