Overcoming Drug Resistance in Lung Cancer

When asked which aspects of her recent research on *KRAS* mutations represent breakthroughs, Barbara Burtness, MD, laughed and said, "In its entirety. It's totally new." Dr. Burtness is a Professor of Medicine (Medical Oncology); Co-Leader of the Developmental Therapeutics Research Program; Disease Aligned Research Team Leader for the Head and Neck Cancers Program; and Interim Associate Cancer Center Director for Diversity, Equity, and Inclusion. She and her collaborator, Jong Woo Lee, PhD, a research scientist at Yale Cancer Center, recently presented their striking findings.

Non-small cell lung cancer (NSCLC) with *KRAS* mutation accounts for about 30 percent of all lung cancers. "They typically have a poor prognosis," said Dr. Burtness, "and until recently there had been no great success in targeting mutated *KRAS*." Recent news has been more encouraging. Two drugs that target *KRAS*-G12C, the most common mutation, have demonstrated response rates of 40 to 50 percent in NSCLCs with the mutation. In May, the FDA approved one of these drugs, sotorasib, for use against these cancers, and in June the agency designated the other drug, adagrasib, as a "breakthrough therapy," which put it on the fast track toward approval.

But this good news comes with an asterisk. The new *KRAS* inhibitors are not effective for very long. In most patients, the lung tumors eventually sidestep the inhibitor and begin to grow again, typically within five months. "It appears to be extremely common for patients to develop acquired resistance," said Dr. Burtness. "There's already a lot of research looking for the mechanisms of resistance."

Drs. Burtness and Lee have been working on a related target, Aurora Kinase A (AURKA), for many years. Knowing that there is a signaling pathway that connects *KRAS* to AURKA and that overexpression of AURKA seems to drive worse outcomes in lung cancer, they pursued the idea of a combination. "We took a lung cancer cell line with *KRAS* mutations and tested a combination of sotorasib and an AURKA inhibitor called VIC-1911," said Dr. Lee, "and we found an effect of really profound synergy." Inhibiting AURKA seems to prevent tumor cells from developing resistance to the *KRAS* inhibitor, and as a result some of the cells begin to die.

Dr. Burtness knew from her work on head and neck cancers, where AURKA is an important target, that the protein kinase WEE1 is also implicated. She and others at Yale had been testing AURKA inhibitors and WEE1 inhibitors alone or in combination on head and neck cancer. The scientists wondered whether inhibiting AURKA and WEE1 simultaneously might replace the need for chemotherapy. Drs. Burtness and Lee began testing that hypothesis five years ago.

"The combination was extremely synergistic, and we have validated it in animal models," explained Dr. Burtness. "We had also started validating it in lung cancer when the *KRAS* drugs became available, and that's one reason we moved so swiftly on this."

When they added the WEE1 inhibitor adavosertib to the AURKA inhibitor VIC-1911 and tested the combination against *KRAS*-mutated lung cancer cells with resistance to sotorasib, the result was what biologists call mitotic catastrophe—extensive cell death.

Drs. Burtness and Lee are currently testing these combinations in animal models, but the need to find a way to overcome resistance to sotorasib is so urgent that the combination is also quickly moving to patients. Yale will host a clinical trial this year involving sotorasib and VIC-1911. Keeping the trial at Yale is important, said Dr. Burtness. "The goal of the Developmental Therapeutics Program is to do basic and translational science that ends up in clinical trials that benefit our patients."

The principal investigator of the clinical trial will be Sarah Goldberg, MD, MPH, Associate Professor of Medicine (Medical Oncology) and Research Director of the Center for Thoracic Cancers. Patients with NSCLC who are resistant to the *KRAS* inhibitor will receive either VIC-1911 alone or in combination with sotorasib. Patients who have not been previously treated with the *KRAS* inhibitor will get sotorasib plus VIC-1911.

As the trial proceeds, Drs. Burtness and Lee will test all these drug combinations on cell models, animal models, and tissue samples from the study's patients. They also think that as more *KRAS* inhibitors come online, the strategy of combining them with inhibitors of AURKA or AURKA plus WEE1 could be effective against other cancers.

"I'm really lucky to work with Dr. Burtness on head and neck cancer and also on lung cancer," said Dr. Lee. "In my career, working at Yale is the first time I could see some translational perspective. I'm a biologist, always working in the lab, but this is one of my dreams—to come here and to see a clinical trial based on my findings."