Dr. Barbara Burtness, MD, has 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 inhibitor of AURKA and that overexpression of AURKA seems to drive resistance to the KRAS inhibitor, and as a result some of the cells begin to die.”

The combination was extremely synergistic, and they have validated it in animal models, explained Dr. Burtness. “We had also started validating it in lung cancer when the drugs became available, and that’s one reason we moved so rapidly on this.”

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Dr. Burtness and Dr. 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 inhibitor of AURKA and that overexpression of AURKA seems to drive resistance to the KRAS inhibitor, and as a result some of the cells begin to die.”

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Dr. Burtness and Dr. 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 the KRAS mutations that respond 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 receive 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 such translational perspectives. I’m a biologist, always working in the lab, but this is one of my dreams—to come here and see a clinical trial based on my findings.”