When asked which aspects of her recent research on KRAS mutations inform breakthroughs, Barbara Burtness, MD, laughed and said, “In its entirety. It’s been a journey. It’s really been a journey.” Dr. Burtness is a Professor of Medicine (Medical Oncology) and Research Director of the Center for Thoracic Cancers. Patients with KRAS mutations have extremely poor outcomes in lung cancer, they pursue the idea of a combination. “We took a lung cancer cell line with KRAS-G12C, the most common mutation, and tested a combination of sotorasib and an AURKA 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 combination was extremely synergistic, and we have validated it in animal models.” Inhibiting AURKA seems to prevent tumor cells from developing resistance to the AURKA inhibitor, and as a result some of the cells begin to die. Dr. 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 AURKA inhibitor, and as a result some of the cells begin to die.

Barbara Burtness, MD

Dr. Burtness has also been validating it in lung cancer when the KRAS drugs became available, and that’s one reason we moved so swiftly on this.”

As the trial proceeds, Drs. Burtness and Lee will test all three 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.”