Seattle, WA, who was not involved in the research, agrees that the finding of metabolically active bacteria within so many human tumors "potentially has huge implications" for understanding and treating the disease. But she wonders whether the high prevalence that the Israeli researchers reported might be an artifact of contaminated paraffin-embedded samples.

"The level of positivity that they're seeing with their imaging was really surprising to me," she says—particularly because they found more evidence of bacteria in tumor samples when using visualization methods than in genomic assays. Although the researchers went to great lengths to control for potential sources of contamination in the genomic data, "it's inherently difficult to control for that when you're imaging archival specimens," Bullman notes.

Regarding the conclusions, "I would be a little bit cautious," she says. However, "if it is reproducible and it's real, it's potentially paradigm shifting for cancer biology." *–Elie Dolgin* ■

Personalized Vaccine Induces Antitumor Activity

A personalized cancer vaccine, when combined with the PD-L1 inhibitor atezolizumab (Tecentriq; Genentech), has shown early efficacy in patients with solid cancers. In a phase Ib trial, the combination induced neoantigen-specific T-cell responses—and elicited complete or partial tumor eradication in some patients. Results were presented at the American Association for Cancer Research Virtual Annual Meeting II: June 22–24, 2020.

Mutated neoantigens are recognized as foreign by the immune system, thus inducing strong T-cell responses. However, most of these mutated neoantigens are not shared among patients, explained Juanita Lopez, PhD, of The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research in London, UK, who presented the results. "Therefore, targeted neoantigen-specific therapy requires an individualized approach."

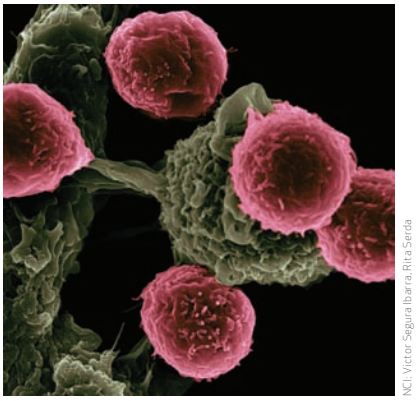
To this end, Lopez and her team tested RO7198457 (BioNTech/Genentech), a neoantigen-specific immunotherapy. The researchers used next-generation sequencing to identify somatic mutations and predict immunogenic neoantigens in each patient. They then encoded up to 20 neoantigens in mRNA molecules to create the vaccine, which is delivered intravenously to antigen-presenting cells—particularly dendritic cells in the spleen. It is thought that RO7198457 enters these cells and activates CD4 and CD8 T-cell responses by prompting the production of proinflammatory cytokines and costimulatory molecules, and by engaging with MHC class I/II molecules.

The trial tested RO7198457 plus atezolizumab in patients with locally advanced and metastatic solid tumors. In the dose-escalation phase, the combination induced the production of proinflammatory cytokines at all dose levels and elicited neoantigen-specific T-cell responses in 46 of 63 patients. These patients had a median of 2.6 neoantigen T-cell responses, determined to be both CD4- and CD8-derived. The combination led to one complete response in a patient with rectal cancer and one partial response in a patient with triple-negative breast cancer who had previously received a PD-1 inhibitor. The patient with breast cancer remains on treatment after 1.5 years.

The expansion cohorts included 144 patients with solid cancers—most commonly non–small cell lung cancer (NSCLC), melanoma, triple-negative breast cancer, and urothelial cancer. Patients received a median of three prior therapies, and 39% received prior immunotherapy. Overall, nine patients responded to the therapy—including one complete response—and 54 more patients experienced stable disease. The combination was well tolerated, with most adverse events classified as grade 1 or 2.

In patients in clinical practice "we often never see any immune cells within the tumor—so that suggests to us that an immune response was never primed or initiated," Lopez said. "The thing that I'm most excited about is that we've managed to show that in the majority of [trial] patients we were able to elicit a specific immune response."

However, Lopez acknowledged that the overall response rate was low, and more research is needed to understand why patients respond and how the vaccine can be improved. She and her team are investigating tumor biology and mechanisms of resistance in a dedicated biomarker biopsy cohort. They are also exploring whether the vaccine may be more beneficial if given earlier in the course of treatment.



NCI, Victor Segura Ibarra, Rita Serda

This scanning electron microscope image shows dendritic cells (in green) interacting with T cells (in pink). It is thought that RO7198457 enters dendritic cells and induces neoantigen-specific T-cell responses.

Two randomized phase II trials will assess whether combining the vaccine with immune checkpoint inhibitors improves outcomes compared with immunotherapy alone: One will test the therapy with atezolizumab as an adjuvant treatment for patients with NSCLC; the other will combine it with the PD-1 inhibitor pembrolizumab (Keytruda; Merck) in patients with newly diagnosed melanoma.

Elaine Mardis, PhD, of Nationwide Children's Hospital in Columbus, OH, who commented on the findings, praised the trial's design wherein the vaccine was given simultaneously with an immune checkpoint inhibitor—a contrast with previous studies that typically administered the vaccine first. "We don't really understand, I would argue, what the right sequence of events is," she added, "and so it's really important to have these trials done, and to have them presented, and to learn from them." *–Catherine Caruso* ■

Tiragolumab Impresses in Multiple Trials

The TIGIT inhibitor tiragolumab (Genentech), alone or in combination with the PD-L1 inhibitor atezolizumab (Tecentriq; Genentech), may be effective against solid cancers. In phase I and II