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."

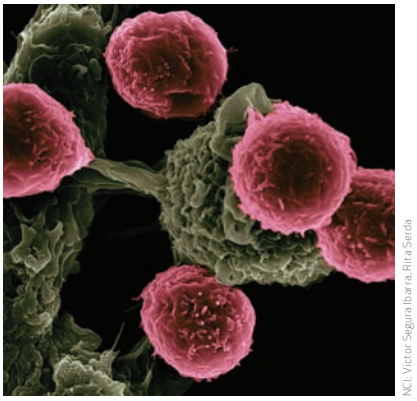
To this end, Lopez and her team tested RO7198457 (BioNTech/Genentech), a neoantigen-specific immunotherapy. The researchers used next-generation sequencing to identify somatic mutations and predict immunogenic neoantigens in each patient. They then encoded up to 20 neoantigens in mRNA molecules to create 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

trials reported at two recent medical meetings, the agent achieved statistically significant results in multiple solid malignancies—most notably non–small cell lung cancer (NSCLC).

TIGIT is a receptor expressed on natural killer cells and T cells. It inhibits immune-cell activity by binding to the PVR ligand on tumor and antigen-presenting cells, and its expression strongly correlates with that of PD-1.

Thus, researchers hypothesized "that anti-TIGIT antibodies, which prevent TIGIT from binding to its ligand, could restore the antitumor response and could complement the activity of anti–PD-L1/ PD-1 antibodies," said Melissa Johnson, MD, of the Sarah Cannon Cancer Institute in Nashville, TN. This hypothesis, she added, is supported by preclinical data suggesting that anti-TIGIT plus anti–PD-L1 agents synergistically improve tumor control and prolong survival compared with either antibody alone.

A phase Ia/Ib trial tested tiragolumab in solid cancers. Alone, the drug led to stable disease in four of 24 patients; together, tiragolumab plus atezolizumab elicited responses in three of 49 patients—including a partial response in head and neck squamous cell carcinoma and partial and complete responses in NSCLC. In an expansion cohort, seven of 14 patients with metastatic PD-L1–positive NSCLC responded to the combination. Results were reported by Johanna Bendell, MD, also of Sarah Cannon, at the American Association for Cancer Research Virtual Annual Meeting II: June 22–24, 2020.

Building on those results, Johnson and her colleagues launched the phase II CITYSCAPE trial, which enrolled patients with newly diagnosed locally advanced or metastatic NSCLC who expressed PD-L1 in at least 1% of tumor cells and did not have *EGFR* or *ALK* alterations. Patients were randomly assigned to receive tiragolumab plus atezolizumab or atezolizumab alone. Johnson reported on 135 patients at the 2020 American Society of Clinical Oncology Annual Meeting, May 29–31.

The combination arm had an overall response rate (ORR) of 37% and a median progression-free survival (PFS) of 5.6 months, compared with 21% and 3.9 months in the atezolizumab arm. This difference was linked to PD-L1 expression: Patients in the combination group with PD-L1 expression of at least 50% had an ORR of 66% and did not reach median PFS, compared with 24% and 4.1 months in the atezolizumab group. In contrast, patients in the combination group with lower PD-L1 expression had an ORR of 16% and a median PFS of 4 months, compared with 18% and 3.6 months in the atezolizumab group.

More than 96% of patients in both groups experienced side effects. In addition, 69% of patients treated with the combination experienced immune-related adverse events—most commonly rash and infusion-related reactions—compared with 47% of patients receiving atezolizumab.

The phase III SKYSCRAPER-01 trial is currently investigating tiragolumab plus atezolizumab in patients with newly diagnosed NSCLC and PD-L1 expression of at least 50%. Early-phase trials are also exploring tiragolumab in cervical cancer and small cell lung cancer, as well as blood cancers.

"What has generated a lot of buzz is the objective response rate seen, which is mainly driven by the PD-L1–high group," said Grace Dy, MD, of Roswell Park Cancer Institute in Buffalo, NY, who provided commentary on the phase II trial. Median PFS also favored the combination, she added, also due to PD-L1–high patients. She cautioned, however, that "while we are all excited by the data and want to see a winner, we should be careful."

Cross-trial comparisons are difficult, Dy said, yet it is worth noting that the atezolizumab control group fared significantly worse than the control groups of other phase III trials in NSCLC, which could have magnified the benefit. She also said she wants to know whether favorable or unfavorable mutations were distributed evenly between groups. For example, preclinical data suggest that DNM1 expression maximizes the effect of TIGIT blockade and may correlate with MHC class I expression.

"Nonetheless," she concluded, "we are cautiously optimistic that the combination is a promising advancement."
–*Catherine Caruso* ■

NOTED

The FDA approved the selective oncogenic transcription inhibitor lurbinectedin (Zepzelca; PharmaMar/Jazz Pharmaceuticals) for adults with metastatic small cell lung cancer who have received platinum-based chemotherapy. The approval, the first for the agent, was based on a phase II basket trial in which 105 patients had an overall response rate of 30% and a median duration of response of 5.1 months.

AbbVie will pay Genmab $750 million up front in a deal that could be worth up to $3.2 billion more in milestone payments. Together, the companies will develop and commercialize three of Genmab's early-stage bispecific antibody candidates, including the CD3/CD20-targeting agent epcoritamab, a CD3x5T4 antibody, and a drug that targets CD37.

Tepotinib may be effective in patients with advanced NSCLC who have *MET* exon 14 skipping mutations (N Engl J Med 2020 May 29 [Epub ahead of print]). In a single-arm phase II study, 46% of 152 patients responded to the drug, and responses lasted a median of 11.1 months.

In a series of talks at the American Association for Cancer Research (AACR) Virtual Annual Meeting II: June 22–24, 2020, **researchers discussed the underrepresentation of minority patients in clinical trials.** Ajay Nooka, MD, MPH, of Emory University in Atlanta, GA, spoke about efforts there to increase participation of Black patients in multiple myeloma trials, and Ruben Mesa, MD, director of the Mays Cancer Center in San Antonio, TX, outlined work in southern Texas to improve accrual of Hispanic patients in all types of cancer trials. Among their strategies: partnering with community-based organizations, providing patients with culturally specific educational materials, and educating clinicians about barriers to trial participation.

Also at the AACR meeting, Jean-Yves Pierga, MD, PhD, of the Institut Curie in Paris, France, spoke about the UCBG COMET trial, which compared the prognostic value of circulating tumor cells with circulating tumor DNA for metastatic breast cancer. He concluded that **the two approaches are more complementary than overlapping**, with both biomarkers providing independent prognostic information and biological insights.

For more news on cancer research, visit *Cancer Discovery* online at http://cancerdiscovery.aacrjournals.org/CDNews.