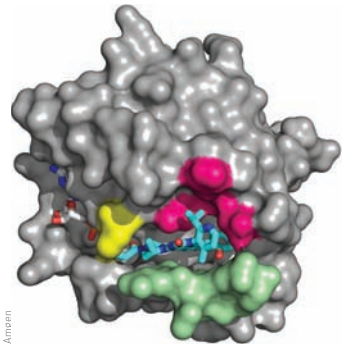


The yellow area indicates where AMG 510 covalently binds to KRAS^{G12C}.

progression-free survival was 4 months across all doses, and 4.2 months for those treated with 960 mg.

David Hong, MD, of The University of Texas MD Anderson Cancer Center in Houston, presented findings from a CodeBreak 100 cohort that enrolled patients with various solid tumors. Of 22 evaluable patients, three—one each with appendix cancer, melanoma, and endometrial cancer—achieved partial responses. In addition, 13 patients had stable disease, of whom three, all with pancreatic cancer, also experienced tumor shrinkage by nearly 30%, Hong observed.

AMG 510's safety profile was similar to what had previously been reported, the investigators said. Mild diarrhea, nausea, and fatigue were the main side effects, and no dose-limiting toxicities were seen.

"The response rate does seem to be lower in colorectal cancer compared to the NSCLC data shown last year," Hong remarked. "This inconsistency suggests that either KRAS^{G12C} is not the dominant driver in colorectal cancer, or other pathways, such as WNT and EGFR, mediate oncogenic signaling beyond KRAS."

Fakih, too, noted "more durable disease control" in the NSCLC cohort, adding that response differences "may be partly related to higher EGFR expression" in colorectal cancer versus NSCLC. Blocking KRAS^{G12C} can lead to compensatory phosphorylation of EGFR, in turn activating the MAPK pathway—and this compensation, being triggered "to a much greater extent in colorectal cancer cells, would mitigate AMG 510's antitumor activity," he explained.

A recent preclinical study has shown just that, pinpointing EGFR signaling as the main route by which colorectal cancer dodges KRAS^{G12C} inhibition (Cancer Discov 2020 May 19 [Epub ahead of print]). In various models, "the addition of an EGFR inhibitor was synergistic," Fakih said. "This has significant implications, suggesting the need for vertical blockade of both EGFR and KRAS to achieve optimal benefit."

As such, researchers have launched the multiarm CodeBreak 101 trial, using a "master protocol approach" that allows "rapid evaluation of different agents in combination with AMG 510, based on solid preclinical rationale," Fakih added. Drugs currently being tested include not only EGFR inhibitors but also SHP2 inhibitors, as well as anti–PD-1 immunotherapies.

Other translational and correlative studies are ongoing, Hong said, because "as of now, we don't have any evidence or data that clearly differentiate responders from nonresponders" to AMG 510.

With more KRAS-targeting contenders on the horizon, too—Mirati Therapeutics' MRTX849, as well as candidates from Revolution Medicines and Oncogenuity—a therapeutic area once considered undruggable is expected to flourish. *–Alissa Poh* ■

Tumors Appear Rife with Bacterial Lodgers

Intracellular bacteria are widespread in different tumor types, forming distinct populations that may play a critical role in shaping the microenvironment of cancers, according to a comprehensive survey of more than 1,000 tumor microbiomes across seven cancer types (Science 2020;368:973–80).

Scientists had previously linked tumor-residing bacteria to carcinogenesis and therapeutic responses, but the phenomenon seemed limited to a handful of pathogenic microbes influencing tumors mostly at mucosal surfaces. The new findings instead suggest that these intratumoral bacterial communities are far more diverse and pervasive, penetrating deep into protected body sites typically considered sterile, such as the brain.

"This is a really important initial step in showing that intratumoral microbes are found all over the body and that they're real—we're not just dealing with contamination, which has been a concern in the past," says Chloe Atreya, MD, PhD, of the University of California, San Francisco, who cowrote a commentary about the research (Science 2020;368:938–9). "It opens a door to a whole other facet of the microenvironment that we hadn't really been considering."

To catalogue the cancer microbiome, a team led by Ravid Straussman, MD, PhD, of Weizmann Institute of Science in Rehovot, Israel, and Noam Shental, PhD, of the Open University of Israel in Ra'anana, quantified bacterial DNA found in 1,010 tumor samples and 516 normal controls. They sequenced 16S ribosomal RNA—a common probe for bacterial detection—and discovered more than 500 bacterial species colonizing tumor tissue, albeit to a different extent in each cancer type and with different mixes of species.

More than 60% of breast, pancreatic, and bone tumors tested positive for bacterial DNA, compared with fewer than 25% of lung cancers, melanomas, and ovarian tumors. In brain cancers, bacterial DNA was detectable in about 45% of samples. The microbiome of breast tumors proved the most diverse of those tested. The authors also documented associations between specific bacteria and tumor type, smoking history, and immunotherapy responses, suggesting that targeting the microbes might improve survival.

The results dovetail with those reported earlier this year by Rob Knight, PhD, and his colleagues at the University of California, San Diego, who showed that signatures of microbial DNA and RNA are pervasive across human tumors (Nature 2020;579:567–74).

However, the Israeli-led team went beyond that earlier finding, notes Eytan Ruppin, MD, PhD, of the NCI's Cancer Data Science Laboratory, who was not involved in either study. In addition to looking at genomic data, Straussman and Shental's group used immunostaining, electron microscopy, and cytogenetic techniques to show that bacteria are mostly found inside cancer and immune cells rather than in the surrounding matrix. "It's a landmark contribution," Ruppin says.

Susan Bullman, PhD, of the Fred Hutchinson Cancer Research Center in

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."

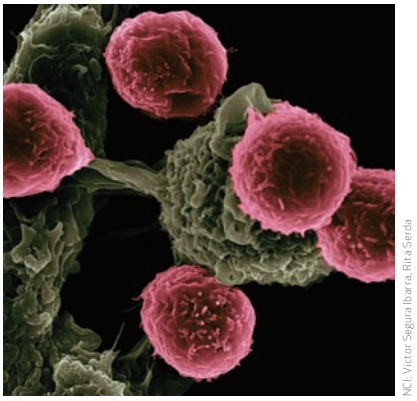
To this end, Lopez and her team tested RO7198457 (BioNTech/Genentech), a neoantigen-specific immunotherapy. The researchers used next-generation sequencing to identify somatic mutations and predict immunogenic neoantigens in each patient. They then encoded up to 20 neoantigens in mRNA molecules to create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