lymphocytes that might suppress the cells. After the infusion, patients receive up to six doses of IL2 to stimulate the restored cells, which infiltrate and attack the tumor. Side effects such as fever, nausea, and cytopenia can result. Finckenstein says that trial participants did not suffer any unexpected adverse effects. However, Iovance did not specify the types or frequencies of side effects.

"These are the most promising results for any adoptive T-cell approach for NSCLC," says John Heymach, MD, PhD, of The University of Texas MD Anderson Cancer Center in Houston, who was not connected to the trial. As the trial progresses, Heymach will be watching for data on response duration and progression-free survival, which will reveal whether patients whose tumors don't shrink still benefit from the treatment.

"While there is activity, it is modest," says Justin Gainor, MD, of Massachusetts General Cancer Center in Boston, who also was not connected to the trial. "We need more information to sort out which patients are most likely to respond to an agent like this."

Additional research may help resolve how effective the TILs are. Two other arms of the IOV-COM-202 trial include patients with NSCLC, and a separate Iovance-sponsored phase II trial is testing LN-145 as a second-line therapy in patients with the disease. *–Mitch Leslie* ■

doi: 10.1158/2159-8290.CD-NB2021-0370

Gut Microbiota May Mediate AEs

Immune-related adverse events (AE), such as colitis, are common and sometimes severe in patients receiving combination CTLA4 and PD-1 blockade. However, what causes these AEs has not been fully established, making it challenging to predict which patients are most at risk for them and to determine optimal solutions. Now, evidence from a recent study suggests that certain types of gut microbes in patients with melanoma may mediate these side effects—and may do so in part via the cytokine IL1β (Nat Med 2021 Jul 8 [Epub ahead of print]).

In 77 patients with advanced melanoma who received combination CTLA4–PD-1 blockade, 93.5% experienced immune-related AEs; 49% of all patients developed grade 3 or higher immune-related AEs. Pretreatment microbiome profiling performed using stool samples from 54 patients for whom specimens were available revealed that severe immune-related AEs were linked to the presence of certain gut bacteria, particularly *Bacteroides intestinalis* and, to a lesser extent, *Intestinibacter bartlettii*.

These results weren't a complete surprise. "Multiple reports by independent groups have linked outcomes of immune checkpoint inhibitor therapy with intestinal microorganisms," says Diwakar Davar, MD, of the University of Pittsburgh in Pennsylvania, who was not involved in the study.

However, investigators were struck by the extent of the relationship. "It was a little bit surprising that the gut microbiota was the strongest association with toxicity in this cohort—stronger than any other factors that we could identify," says Jennifer Wargo, MD, of The University of Texas MD Anderson Cancer Center in Houston, co–senior author of the paper with Laurence Zitvogel, MD, PhD, of the Gustave Roussy Comprehensive Cancer Institute in Villejuif, France.

This finding was validated in a second cohort of 45 patients treated for advanced melanoma. In this group, *B. intestinalis* was exclusively identified in pretreatment stool samples from patients who developed immune-related side effects.

In vivo experiments provided additional credence to the correlation between *B. intestinalis* colonization and immune-related AEs. Researchers treated mouse models of sarcoma and melanoma with antibiotics to ablate their normal microbiota prior to inducing recolonization with *B. intestinalis* and initiating combined immunotherapy. They found that the mice developed intestinal toxicity. Previous research suggested that commensal gut microbes can cause colitis through a mechanism driven by the inflammation-linked cytokine IL1β. Thus, the group gave the mice the FDA-approved IL1 receptor antagonist anakinra (Kineret; Sobi), which substantially diminished gut inflammation.

If validated, the finding that *B. intestinalis* mediates immune-related AEs in patients treated with combined immune checkpoint blockade could inform treatment. For example, clinicians could choose other therapies for patients with significant *B. intestinalis* colonization—or attempt to decrease colonization, for example, with selective bacteriophage treatment—before starting immunotherapy. "Our hypothesis is that by therapeutically targeting and depleting *B. intestinalis*, we could actually abrogate toxicity and preserve response to treatment," Wargo says.

Another potential technique may be to target the proposed mechanism for immune-related AEs by blocking IL1β signaling. However, this method should be approached with caution because IL1β is also involved in pathways that mediate antitumor T-cell function, so preventing IL1β signaling may have the unintended consequence of suppressing therapeutic response.

A further option is fecal microbiota transplant, a procedure that has gained traction for multiple conditions despite varying levels of evidence for its efficacy. All of these approaches will require investigation in randomized clinical trials, yet Wargo is hopeful: "We're going to get tractable strategies to modulate either gut microbes or metabolites that will actually make a meaningful difference." *–Nicole Haloupek* ■

doi:10.1158/2159-8290.CD-NB2021-0371

Genomics Sharpens Risk Stratification for Rhabdomyosarcoma

Mutations in *TP53* and *MYOD1* correlate with shortened survival for