The TILVANCE-301 Trial: Expanding a Patient's Own Tumor-Fighting Cells to Treat Advanced Melanoma

Read about tumor-infiltrating lymphocyte therapy in advanced melanoma and current research directions, including the ongoing TILVANCE-301 trial.

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Cancer immunotherapy is treatment that helps increase the immune system's ability to detect and attack cancer cells. Immunotherapies, specifically immune checkpoint inhibitors (ICIs), are approved for advanced melanoma in the first-line or treatment-naïve setting and have revolutionized melanoma care and the research landscape. However, many metastatic melanoma patients who receive ICI treatment will still experience recurrence or progression of their cancer within about a year. Thus, new and better treatment options are needed to keep melanoma from progressing for a much longer time.

What Are TILs?

Tumor-infiltrating lymphocytes (TILs) are cancer-fighting immune cells that have recognized and surrounded the tumor. However, their presence alone is often not enough to get rid of the tumor.

TIL therapy is cell-based immunotherapy treatment that is derived from the patient's own cancer-fighting immune cells. For TIL therapy, a tumor is surgically removed. Then, the lymphocytes in the tumor are grown in large numbers in the lab. Meanwhile, the patient undergoes chemotherapy to deplete their remaining lymphocytes and make room for the new tumor-fighting lymphocytes. Once enough TILs have been grownin the lab, they are infused back into the patient, along with an immune-boosting drug called interleukin-2 (IL-2).

To learn more about TIL therapy in advanced melanoma and current research directions, including the ongoing TILVANCE-301 trial, we talked to Stephanie Goff, MD, senior research physician in the Center for Cancer Research at the National Cancer Institute (NCI).

How are New Treatments or Treatment Combinations for Melanoma Tested?

New treatment options are first tested in clinical trials, which are research studies that involve

human volunteers. Patients are encouraged to consider all their treatment options, including discussing with their physician the potential of enrolling in a suitable clinical trial. In a recent MRA Meet Up, advanced melanoma patient advocate Jamie Goldfarb, who participated in a clinical trial for TIL therapy, would like patients to know, "A clinical trial should be seen as a treatment option. It should be seen as the best chance of getting the most cutting-edge treatment and not as a last-ditch effort."

In clinical trials, there are three phases of testing focused on evaluating the treatment's effectiveness and safety. In Phase 1, researchers conduct first-time testing of a treatment to determine safe dosage amounts, identify side effects, and evaluate early evidence of efficacy. In Phase 2, testing expands to a larger group of patients following the doses that appeared most promising from Phase 1 testing. Researchers continue to check for safety and side effects, but focus more on determining whether the treatment works. In Phase 3, the trial expands to hundreds, sometimes thousands, of patients. Some patients receive the experimental treatment either alone or in combination with the standard therapy, depending on the trial design. Others may get the standard therapy by itself. The goal of Phase 3 is to collect data on effectiveness, safety, and side effects to ultimately request regulatory approval from government agencies like the FDA.

Amtagvi is Approved for Patients with Melanoma Who Have Received Prior Immunotherapy

Lifileucel (Amtagvi), a one-time TIL therapy treatment, is FDA approved for patients with metastatic melanoma who received prior treatment with an ICI (as well as a BRAF inhibitor with or without a MEK inhibitor in patients with aBRAF^{V600} mutation) and had their cancer progress. This approval was based on results from the Phase 2 C-144-01 trial (NCT02360579), which showed that 31% of patients responded to treatment, including shrinking tumors or disappearance of the cancer.

When comparing TIL therapy to the current standard of care, TIL therapy can provide a more long-lasting, complete response than standard ICI treatments. Dr. Goff stated that in one of their studies at the NCI, 46 of 48 patients with a complete response to TIL therapy never needed another treatment for their melanoma. A response lasting more than 10 years occurs in about a quarter of patients, and a completely curative, lifelong response is possible. Investigations are underway to understand why some patients do not respond.

In the recent MRA Meet Up, Dr. Young Ki Hong of Cooper University Health Care shared, "TIL therapy is very unique, and I would argue, is the most personalized treatment you can get."

Testing TIL Therapyin the First-Line Setting

As noted, lifileucel is currently FDA approved for patients whose melanoma hasn't responded – or quit responding – to PD-1-based immunotherapies and BRAF/MEK targeted therapy (if their

melanoma has the BRAF mutation) but Dr. Goff noted that “TIL therapy is likely even more powerful in the first line setting,” in part because currently approved first-line therapies (the first set of treatments after an advanced melanoma diagnosis) may inhibit some aspects of immune function when given in the second line. The effectiveness of TIL therapy as the very first treatment after a metastatic melanoma diagnosis is an important area of discussion and is currently under investigation.

The Phase 2 IOV-COM-202 trial (NCT03645928) studied the combination of lifileucel and pembrolizumab as first-line treatment in patients with unresectable or metastatic melanoma. Results presented in 2024 showed that more than two-thirds of patients responded to treatment and saw their tumors shrink or disappear. In many patients, responses are sustained over time.Two-thirds of patients are continuing in the study with an ongoing response.

The TILVANCE-301 Clinical Trial Testing Lifileucel with or without Pembrolizumab as First-Line Treatment

Supported by data from the Phase 2 IOV-COM-202 trial, Iovance’s Phase 3 TILVANCE-301 trial (NCT05727904) is currently enrolling patients with Stage 3 or 4 unresectable or metastatic cutaneous, mucosal, or acral melanoma to test lifileucel as first-line treatment in combination with pembrolizumab compared to pembrolizumab alone. Patients in the pembrolizumab-only group may be allowed to receive lifileucel if their cancer progresses. Dr. Goff stated that in a forthcoming publication, it appears that patients with acral melanoma have a similar response rate to TIL therapy as those with non-acral melanoma.

The goal of TILVANCE-301 is to understand more about the safety of lifileucel in combination with pembrolizumab compared to pembrolizumab alone and the efficacy of the combination when used as the very first treatment for metastatic melanoma.

What are theAdvantages and Challenges of TIL Therapy?

Dr. Goff said that a big advantage of TIL therapy is the chance of developing a long-lasting treatment response witha single infusion of TILs. She likened TIL therapy to “stepping up to bat and swinging for a home run.” Also, TIL therapy is personalized with manageable safety considerations. TIL therapy can treat tumors located anywhere with a blood supply, including the brain, bone, and large tumors, although caution is needed in some patients with melanoma that has spread to the brain.

One challenge of TIL therapy involves possible side effects from IL-2 and lymphodepletion. At the first sign of severe side effects, doctors will back off. Some IL-2 is probably beneficial, and the optimal dosing is being studied. These side effects are manageable, short-lived, and usually gone before the patient goes home from the hospital. There are other challenges. TIL therapyis not an immediate treatment, as it takes a few weeks to grow the TILs. The safest place to give TILs and IL-2 is in a hospital, and access may be an issue because not every hospital has personnel that are

appropriately trained to administer TIL therapy right now. Also, TIL therapy may not be appropriate for every person, particularly those (of any age) with poor heart and lung function.

In conclusion, Dr. Goff understands that newly diagnosed patients encounter many challenges and that it may be easier to do a quick treatment such as an ICI. Because ICIs have revolutionized treatment for advanced melanoma, some physicians may hesitate to not offer those drugs as first-line treatment. However, she encourages patients to slow down and talk to their doctor about their options for their first treatment. TIL therapy offers the possibility of a complete, long-lasting response following a “one and done” treatment, rather than needing to go for periodic infusions of an ICI over many months or years.

To learn more about the TILVANCE-301 trial, including who can participate, study locations, and other information and resources, visit clinicaltrials.gov.

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