

Investigating CAR-T Cell Therapy for Advanced Melanoma

An interview with Anusha Kalbasi, MD, a radiation oncologist who studies CAR-T therapy to treat advanced melanoma, a type of skin cancer

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One of the greatest scientific breakthroughs in melanoma research has been the FDA approval of cancer immunotherapy treatments called checkpoint inhibitors. These treatments stimulate the body's own immune system to fight off melanoma. Checkpoint immunotherapies, first approved in melanoma, are now being used to treat a number of different cancer types.

While the implementation of immunotherapy drugs as a standard of care for advanced melanoma has been regarded as a success and offers tremendous hope to patients, there are still patients who do not benefit. In fact, nearly 50% of patients with advanced melanoma either do not respond or develop resistance to immunotherapy treatment.

Every day, researchers are hard at work developing new and improved treatment options for melanoma patients.

CAR-T Cell Therapy to Treat Melanoma

One treatment that is an exciting area of research is CAR-T cellular therapy. Cellular Therapy, also called Cell-based therapy, is a type of immunotherapy cancer treatment that involves the use of living cells to treat or prevent diseases. It is a rapidly evolving field in medicine that holds great promise for various conditions, including the treatment of melanoma and other cancers.

Cell-based therapies can involve the use of different types of immune cells, such as T lymphocyte cells, natural killer (NK) cells, or dendritic cells which play important roles in the immune response against cancer. These different cell-based therapies are an active area of research for the potential treatment of cancer.

In melanoma, the first Tumor-Infiltrating Lymphocyte (TIL) Therapy called Amtagvi (lifileucel) earned FDA approval in early 2024. Over the last several years, genetically modified immune T-cell based therapies called Chimeric Antigen Receptor therapies (CAR-Ts) have been approved for

the use in different types of blood cancers and are being tested in clinical trials in melanoma.

Clinical Trial Testing CAR-T Cell Therapy

Researchers at Stanford University are currently enrolling patients into their [phase I trial \(NCT04119024\)](#) studying CAR-T cell targeting IL13Rα2 for advanced treatment-refractory melanoma. Anusha Kalbasi, MD, Associate Professor of Radiation Oncology, is leading this trial at Stanford along with colleagues Antoni Ribas, MD, PhD, Professor of Medicine at the David Geffen School of Medicine at UCLA and Christine Brown, PhD, Deputy Director of the T Cell Therapeutics Research Laboratory at Beckman Research Institute of City of Hope.

In their study, the CAR-T cells target IL13Rα2, which is a protein expressed on the surface of certain cancer cells, including metastatic melanoma. The presence of IL13Rα2 on the surface of cancer cells indicates whether CAR-T cells may be effective as treatment. IL13Rα2 is expressed in approximately 25% of melanoma patients. A patient's individual expression of IL13Rα2 can be measured by immunohistochemistry (IHA H-score), and the trial includes patients with an IHA H-score of 50 or higher. Approximately 10-15% of patients with melanoma have extremely high expression of IL13Rα2.

We recently spoke with Dr. Kalbasi to learn more about the phase I trial and CAR-T cell therapy as an emerging therapeutic option for patients with advanced melanoma. This trial is funded, in part, from a Team Science Award to Dr. Antoni Ribas (UCLA), Dr. Kalbasi, and colleagues.

How does CAR-T cell therapy work? What makes it unique regarding the melanoma standard of care?

CAR-T cell therapy is a treatment that utilizes a patient's T cells — the key assassin of the immune system — to recognize and kill cancer cells. It typically involves collecting and genetically modifying a patient's own T cells to express a synthetic molecule called a chimeric antigen receptor (CAR), which specifically recognizes cancer cells but not normal cells in the body. The genetically modified T cells are infused back into the patient, where they target and destroy the cancer cells expressing IL13Rα2.

This therapy is unique in melanoma because it directly targets specific proteins expressed on the surface of cancer cells, bypassing some resistance mechanisms that affect standard treatments like immune checkpoint blockade (ICB), which targets proteins on the inside of the cell. CAR-T cells can potentially be effective when ICB fails because the CAR-T cell has a different mechanism of action compared to ICBs.

What question(s) is this trial seeking to answer?

The trial aims to determine the safety of CAR-T cells targeting IL13Rα2 when given intravenously in patients with metastatic melanoma and other solid tumors expressing IL13Rα2. Other studies

have tested giving these CAR-T cells directly into the brain for certain brain tumors, but this will be the first to deliver the treatment systemically. The study also seeks to identify signals that show that the treatment is effective.

What preliminary findings or research led toward the trial?

These CAR-T cells targeting IL13Ra2 were originally developed to treat glioblastoma, a lethal brain tumor. Clinical studies of IL13Ra2 CAR-T cells administered directly into the brain have been performed with encouraging results. We observed that IL13Ra2 is also highly expressed on tumor samples from patients with melanoma and other tumors outside of the brain, like neuroendocrine tumors and thyroid cancers. In the laboratory, we showed that IL13Ra2 CAR-T cells are able to recognize and kill melanoma cell lines and prolong survival in mouse models, and that IL13Ra2 has very low expression on normal cells throughout the body. Based on this we moved forward to conduct a phase 1 trial.

What led to the hunch about this protein being targetable? Knowing that it can be present in melanoma as well as solid tumors, is it driven by something?

The idea of targeting IL13Ra2 stemmed from observing that this protein is predominantly present in cancer cells, including melanoma, and rarely in normal cells. This specificity makes the IL13Ra2 an ideal target for CAR-T cell therapy, by reducing the risk of off-target effects. However, we do not have great insight yet into why certain cancer cells express IL13Ra2 and why others do not.

How could the success of this trial impact the melanoma research landscape?

Success in this trial could establish CAR-T cell therapy as a viable treatment option for patients with metastatic melanoma and other solid tumors, especially those who do not respond to current treatments like ICB. Achieving our aims and milestones will not only pave the way for a phase 2 clinical trial but also establish a multi-institutional model for conducting T-cell therapy studies across California.

Can you describe the impact the MRA team science award had on advancing your research to this point?

High-risk high-reward studies like ours are very difficult to fund through conventional research funding mechanisms. Early support from the MRA Team Science Award was critical to provide us the runway to initiate the clinical trial and generate valuable data from patients that we could leverage for further funding. As a result of this data, we secured a \$10.2 million grant from the [California Institute of Regenerative Medicine](#) to continue the study — this would not have been possible without MRA.

Can you speak to the importance of clinical trials and patient volunteers?

Clinical trials are essential for developing new treatments and ensuring their safety and efficacy. They provide critical data that can lead to FDA approval and wider availability of innovative cell therapies. Participation in clinical trials contributes valuable scientific knowledge, which helps to advance medical research while providing hope and potential benefits for future patients. Additionally, patient volunteers play a vital role in patient advocacy, helping to raise awareness and support for ongoing research efforts.

Why should patients consider a clinical trial as a viable treatment option?

Patients should consider clinical trials as they offer access to cutting-edge therapies that are not yet widely available. For patients with advanced melanoma who have exhausted standard treatments, clinical trials provide an opportunity to receive potentially effective therapies that could improve their outcomes and quality of life. And finally, clinical trials provide a means to help future patients through science and research.

Learn more about Stanford's [CAR-T Clinical Trial](#) which is currently enrolling patient volunteers, including [pre-screening information](#).

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