Melanoma Clinical Trials to Watch: Summer 2025

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August 8, 2025 By Melanoma Research Alliance

The melanoma field is building an arsenal of immune therapies, with several that are currently approved and others that are being tested for patients with advanced disease. In addition, some are being used in the adjuvant (treatment following surgery) or neoadjuvant (treatment before surgery) settings. The approved immune therapies can be categorized into different classes, depending on the way they activate the immune system and enable the immune cells to identify and destroy melanoma cells. The different classes include:

- Cytokine therapy (ie: interleukin 2 or IL-2; aldesleukin)
- Immune checkpoint inhibitors (anti-PD-1, anti-CTLA4, anti-LAG3 antibodies, and combinations)
- Oncolytic viral therapies (T-VEC)
- Bispecific proteins that form bridges between tumor and immune cells (Tebentafusp)
- Cell-based therapy, commonly referred to as tumor infiltrating lymphocytes (TILs)

Many of the immune therapies that were pioneered in melanoma are now being used or tested in more than 30 types of other cancers.

Despite this incredible progress, about 50% of patients will not benefit from these new treatment options. This has created a sense of urgency to make improvements in existing immune therapeutic approaches or identify new ways to activate the immune system. Over the last few years, encouraging early clinical trial data has enabled the advancement of several of these new investigational (not-approved) immune therapies into phase 2 and phase 3 clinical trials for further testing. The goal of phase 2 and phase 3 trials is to collect data on the treatment's effectiveness, safety, and side effects in larger numbers of patients. In this Melanoma Clinical Trials to Watch series, we will discuss three different trials open to enrolling patients: one testing a new immune checkpoint combination and the other two exploring different cell-based therapy approaches.

New Checkpoint Combination: Phase 3 Harmony Head to Head Trial

Immune cells express checkpoint molecules that put brakes on the immune system's ability to find and kill cancer cells. Immune checkpoint inhibitors (ICIs) are antibody treatments that bind to and block these checkpoints so that the brakes are released and the immune cells can then destroy cancer cells. Different ICI therapies have been developed for three well-characterized immune checkpoints: PD-1, CTLA-4, and LAG-3. ICIs such as pembrolizumab (Keytruda) and nivolumab (Opdivo) are approved drugs that block the immune checkpoint molecule PD-1. They are each approved for use in advanced and metastatic melanoma and as adjuvant treatments for resectable melanoma.

Combinations of anti-PD1 drugs with other immune checkpoint drugs have been tested to see if they have better anti-tumor killing activity together than treating with the anti-PD-1 drug alone. Based on results from a phase 2/3 clinical trial, the combination of nivolumab with relatlimab, the latter blocking the LAG-3 checkpoint, was FDA approved for use in patients with advanced melanoma in 2022.

The biotechnology company Regeneron is testing the combination of a novel LAG-3-blocking drug called fianlimab and a PD-1-blocking drug called cemiplimab (Libtayo® that is approved for use in other cancers). A phase I clinical trial (NCT03005782) was conducted that examined the combination of fianlimab and cemiplimab in patients with advanced melanoma. Of the 98 patients treated, 57% of patients responded (meaning tumor shrinkage), and 25% had a complete response, meaning their cancer disappeared. Safety of the fianlimab and cemiplimab combination was similar to that of other single-agent anti-PD-1 therapies.

Based on the encouraging phase 1 data, a phase 3 Harmony Head to Head trial (NCT06246916) is determining how safe and effective the combination of fianlimab and cemiplimab is (the study drugs) compared to the approved combination of relatlimab and nivolumab. The trial is open and enrolling patients who are:

- 18 years and older
- Have advanced melanoma that cannot be removed with surgery (unresectable; Stage 3) or have melanoma that has spread to other parts of the body (metastatic; Stage 4)
- Have NOT received any prior systemic treatments

As with any clinical trial, patients must provide informed consent, which demonstrates their willingness to participate in the study. Patients are then screened by answering questions about their health and medical history as well as undergo tests to see if they qualify to be on this clinical study.

Eligible patients will be selected by chance to receive either:

- The combination of fianlimab and cemiplimab given together every 3 weeks or;
- The approved combination of relatilimab and nivolumab every 4 weeks.

Study participants will continue to be treated depending on how well the drugs are working and if they are having any side effects, which will be assessed from regularly scheduled medical visits.

Approximately 560 patients are expected to be enrolled in the Harmony Head to Head trial, and it is currently open at 96 locations between the U.S. and Canada. Find out more information about this trial.

New Cell Based Therapy Approaches

Cellular therapies involve the use of living cells to help improve the way a patient's immune system responds to and fights cancer cells in the body. In 2024, the first cellular therapy to be approved for use in a solid cancer, more specifically in melanoma, was AMTAGVI (lifileucel). AMTAGVI is a tumor infiltrating lymphocyte (TIL) therapy and uses T-lymphocyte cells that are isolated from surgically removed tumor tissue. These cells are then multiplied in a laboratory a billion-fold and activated before being infused back into the patient. Before the T cells can be infused back into the patient, the patient will undergo a conditioning regimen of chemotherapy (called lymphodepletion), which helps to suppress the patient's immune system and create space for the infused T cells to expand and function effectively. After infusion a certain number of doses of the cytokine IL-2 (aldesleukin) is administered to activate the infused T cells.

Next Generation TILs: Agni-01 Trial

New versions of TILs are being developed that require some modifications (engineering) of the isolated T cells before infusion back into patients. The company Obsidian is engineering a TIL therapy (OBX-115 TIL) that comes armed with a protein called IL15 that becomes expressed on the surfaces or membranes of the engineered TILs (membrane-bound IL15 or mbIL15). mbIL15 has the potential to improve the anti-tumor activity of the modified TILs and lead to longer responses. In addition, the expression of mbIL15 in TILs can be regulated by administration of an FDA-approved drug called acetazolamide (ACZ) which allows activation of the infused T cells. ACZ can be given to boost the function of the TILs when needed and reduced if side effects occur. It also replaces the need for IL-2 infusion used after administration with unmodified TIL therapy which some patients cannot tolerate.

Promising data was presented at the 2025 American Society of Clinical Oncology annual conference on results from the Agni-01 phase 1/2 trial (NCT06060613), which tested the regimen of OBX-115 TIL in patients who did not benefit from immune checkpoint inhibitor therapy (ICI-resistant). Phase 1 trials through a dose escalation select the dose of a drug that should be used in the phase 2 trial, the latter focusing on efficacy and further safety evaluation. Six patients were

treated at the dose selected for the phase 2 portion of this trial, with a 67% response rate including one with a complete response (total tumor disappearance).

The phase 2 portion of the Agni-01 trial is open to enrollment at nine U.S. sites. Patients are eligible to be considered for this trial if they are 18 years and older (no upper age limitations) and if they have melanoma that is not responding or has progressed through ICI treatment. Treatment involves the following steps:

- Tumor procurement by surgery or biopsy to isolate TILs
- Low dose lymphodepletion to suppress the immune system
- Modified TIL (engineered with mbIL15) infusion back into patients with ACZ drug administration

TCR-T Cell Based Therapy- SUPRAME Phase 3 Trial

TCR-T cell-based therapy is a form of cancer immunotherapy where T cells, isolated from a patient's blood, are modified or engineered to express a protein on the surface of the isolated T cells called a T-cell receptor (TCR) that recognizes cancer-specific protein fragments called peptide antigens. The peptide antigen is bound to a special marker called HLA-A*02:01 and the complex is presented on the surface of the tumor cells. The T-cell receptor that was engineered into the patient's T cells recognize this peptide antigen/marker complex. The engineered T cells are then infused back into the patient to target and kill cancer cells.

The biotech company Immatics is developing a TCR-T therapy (IMA203) targeting the protein PRAME that is highly expressed in multiple solid tumors, including melanoma. The engineered PRAME TCR-T recognizes PRAME-specific peptide antigens linked to the marker HLA-A*02:01 that is displayed on the surface of tumor cells. The PRAME TCR-T is then prompted to kill the tumor cells.

The results of follow-up from a Phase 1b trial administering a one-time infusion of the IMA203 PRAME cell therapy to 33 patients with metastatic melanoma that did not have success with prior therapies showed favorable tolerability and promising clinical activity. A cORR rate, defined as sustained shrinkage or disappearance of melanoma, of 56% was observed in the 33 patients. Almost half of the patients receiving treatment and follow-up had cutaneous (skin) melanoma and the other half had uveal melanoma (melanoma of the eye). The cORR rates were 50% and 67%, respectively, for each melanoma subtype.

The SUPRAME Phase 3 trial (NCT06743126) is now open in the U.S. and Germany and is enrolling patients with cutaneous melanoma that is unresectable (melanoma cannot be surgically removed) or metastatic (has spread to other parts of the body). HLA testing must also be performed, as participants must be positive for the HLA-A*02:01 marker. Patients with acral melanoma can also be included if they meet the eligibility criteria.

There will be two treatment groups in this study. Eligible patients will be enrolled by chance either into:

Group 1: Patients receiving the IMA203 regimen; or

Group 2: Patients receiving investigator's choice of selected approved therapies.

The IMA203 regimen is administered in the following way:

- A patient's T cells are obtained from their blood in a process called leukapheresis
- T cells are then engineered to express the PRAME-specific T cell receptor
- Patient's receive lymphodepletion to suppress their immune system
- PRAME directed T cells are infused back into the patient (one-time)
- Low-dose IL-2 infusion is administered

More information on immune and cellular therapies can be found on the MRA website.

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