Melanoma Clinical Trials to Watch: December 2023

Lack of awareness of and participation in clinical trials are the biggest obstacles to bringing new skin cancer therapies to market.

December 28, 2023 By Melanoma Research Alliance

Treatment of advanced melanoma has dramatically improved over the past decade with 16 new therapies approved by the Food and Drug Administration (FDA). Even with these treatment advances, 50% of patients with advanced melanoma will either not respond to any of these treatments or their disease will progress creating a critical need to find new therapies.

Clinical trials are designed to test new treatment approaches, help advance melanoma research, and aim to improve future treatment options so that all patients may benefit. Lack of awareness of and participation in clinical trials are the biggest obstacles to bringing new therapies to market. MRA's Melanoma Clinical Trials to Watch series aims to raise awareness of clinical trials by regularly highlighting trials that are currently recruiting patients and featuring others that have recently shared promising updates.

New Oncolytic Virus Combos Show Encouraging Preliminary Results

Oncolytic viruses are a type of immunotherapy that can kill tumor cells and modify immune cells in the tumor microenvironment to elicit an anti-tumor immune response when injected directly into tumors. Because the stimulated immune cells circulate throughout the body, the anti-tumor effects are not only seen in the injected tumors but spread systemically to non-injected tumors elsewhere in the body, commonly known as the abscopal effect.

T-VEC (Imlygic) is an FDA approved oncolytic virus therapy that preferentially infects and kills cancer cells over normal cells and also enhances the immune system's ability to fight cancer. It is made from a genetically modified herpes virus (cold sore virus) and was approved in 2015 to treat patients with Stage III and IV melanoma who have tumors that can be directly injected but are not able to undergo surgery (referred to as unresectable melanoma).

Hoping to improve upon T-VEC, researchers at Replimune have developed a genetically modified version of the herpes virus that they call RP1. RP1 appears to be even more selective toward tumor cells, and early trials show it generates a strong anti-tumor immune response.

Replimune is currently enrolling patients in a clinical trial testing the combination of RP1 with the anti-PD1 immune checkpoint drug Opdivo (nivolumab), in patients with cutaneous melanoma who have failed prior checkpoint therapies. The company presented early data in June at the American Society for Clinical Oncology (ASCO) conference and provided an update on this cohort in December that showed the experimental combination had an overall response rate (measuring tumor shrinkage) of 31.4% with the majority of responses being durable.[1,2]

Furthermore, the combination had an acceptable safety profile. Responses were often observed among not only the injected tumors but in non-injected tumors elsewhere in the body, suggesting an abscopal effect.

Replimune is also testing a second oncolytic virus that they call RP2. RP2 has the same tumor killing and immune stimulating features of RP1 but also expresses a molecule that can recognize the immune checkpoint CTLA-4 on immune T cells in the local tumor environment, activating these cells' tumor killing potential. Dr. Joseph Sacco (University of Liverpool and Clatterbridge Cancer Centre, UK) presented data at the 20th International Congress of the Society of Melanoma Research in early November testing RP2 as a single agent or in combination with nivolumab in patients with metastatic uveal melanoma. Uveal melanoma, also known as ocular melanoma, is a rare form of melanoma that has limited treatment options and is not very responsive to immune therapies. Out of 17 patients treated, 5 patients responded (overall response rate of 29.4%) with one patient only receiving RP2 monotherapy and the other four patients treated with RP2 combined with nivolumab. Responses were observed in patients with liver, lung, and bone metastases who had received prior checkpoint inhibitor therapy with some responses seen in both injected and non-injected tumors.

Tumor-Infiltrating Lymphocyte (TIL) Therapy Awaits FDA Approval Decision

Tumor infiltrating lymphocyte (TIL) therapy, first pioneered by Dr. Stephen Rosenberg from the National Cancer Institute, isolates immune cells called lymphocytes from a patient's surgically removed tumor that are then grown in large quantities in the lab. The army of grown TILs are then reinfused back into the patient where they recognize and destroy cancer cells in the body. Prior to the reinfusion, the patient is treated with chemotherapy to deplete all existing lymphocytes. After TIL reinfusion, the patient is treated with a therapy that encourages lymphocytes in the body to grow and divide.

Iovance Biotherapeutics has a proprietary TIL manufacturing process that is being used to develop an individualized TIL therapy called Lifileucel. It is being tested in advanced unresectable or metastatic melanoma patients who have progressed on or after treatment with checkpoint immunotherapy and/or BRAF/MEK targeted therapy. Recent data presented at the Society for Immunotherapy of Cancer (SITC) annual conference demonstrated durable efficacy and a 4-year overall survival rate of 21.9% in this advanced and difficult to treat patient population.[3]

Included in the above study is a small group of patients with mucosal melanoma, a rare melanoma

subtype that develops in the mucous membranes of the body. Mucosal melanoma accounts for only 1% of all melanomas diagnosed and represents a difficult to treat subtype of the disease. Preliminary data was presented by Dr. Evido Domingo-Musibay (Masonic Cancer Center) at the 2023 European Society of Medical Oncology Annual Congress and by Dr. Harriet Kluger (Yale Cancer Center) at this year's Society for Melanoma Research Annual Congress from 12 patients with advanced mucosal melanoma that were refractory to anti-PD1 treatment. These patients had an overall response rate of 50% (6 out of 12 patients) with durable responses in 4 patients from a single infusion of Lifileucel.[4] Researchers plan to follow these patients for a number of years to look at the true durability of response.

On March 24, 2023, Iovance submitted a Biologics License Application (BLA) to the FDA for the approval of Lifileucel. The FDA decision is expected by the end of February 2024.

Now Recruiting: Novel Immunotherapy Combination Being Tested in the Neoadjuvant Setting

In melanoma, drug therapy is sometimes given after surgery to reduce the risk of melanoma from returning. This type of treatment, called adjuvant therapy, is being increasingly used in patients that may be at high risk for their melanoma to come back. Another approach, called neoadjuvant therapy, is being explored where systemic treatments are given before surgery to see if the tumor and lymph nodes respond. By giving the drugs first, then completing the surgery, doctors can then examine the tumor tissue following surgery to assess how well the tumor responded to the treatments. In addition, administering therapy before surgery, while the tumor is still present, may elicit a more robust systemic antitumor immune response.

A pivotal phase 2 trial, SWOG S1801, found that PD-1 checkpoint inhibitor pembrolizumab improved event-free survival at 2 years when given before surgery (neoadjuvant therapy) as compared with giving it after surgery (adjuvant therapy) for patients with stage III melanoma.

Another cutting-edge clinical trial testing neoadjuvant therapy is the phase 2 NeoACTIVATE (NCT03554083) trial. Arm C of the trial is still actively recruiting patients with stage III melanoma that are at high risk of recurrence at the following clinical sites: Mayo Clinic, Jacksonville, Florida (855-776-0015); Mayo Clinic, Rochester, Minnesota (855-776-0015); University of Minnesota, Masonic Cancer Center, Minneapolis, Minnesota (612-625-8942).

"NeoACTIVATE brings the exciting approach of neoadjuvant therapy to patients with stage III advanced melanoma," noted Tina Hieken, MD, a surgical oncologist at the Mayo Clinic Rochester. "We believe that Arm C of the trial, which combines the approved immune checkpoint inhibitor drug atezolizumab (targeting PDL1) with the novel treatment tiragolumab (targeting the protein TIGIT), is an innovative approach that could lead to higher responses, with fewer side effects, in the pre-surgical, neoadjuvant setting."

Patients diagnosed with an advanced melanoma should consider discussing a neoadjuvant clinical

trial with their doctor before they plan to have surgery.

This blog post was published by the Melanoma Research Alliance on December 13, 2023. It is republished with permission.
