IGNYTE-3 Trial: Harnessing the Power of Viruses to Activate the Immune System and Treat Advanced Melanoma

Oncolytic viruses are a form of immunotherapy that uses viruses to infect and destroy cancer cells, including advanced skin cancer.

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Although treatment options for advanced melanoma have improved, many patients still will not benefit from currently approved therapies. In particular, some patients treated with anti-PD1 immunotherapy never respond (called primary resistance) and others initially respond and then their disease progresses (called secondary resistance). Limited treatment options are available for such patients, representing a clear unmet medical need for patients today.

Oncolytic viruses are a form of immunotherapy that use viruses to infect and destroy cancer cells. This type of immunotherapy is under investigation to treat advanced melanomas and may be useful when initial anti-PD-1 immunotherapy stops benefiting patients. These viruses can elicit a local inflammatory reaction and can also carry a payload of immune active medications. In the wake of the Food and Drug Administration's (FDA) 2015 approval of the first oncolytic virus treatment for melanoma called Imlygic (talimogene laherparepvec, or T-VEC), researchers have been trying to improve the effectiveness of this type of treatment to localized tumors as well as to tumors that have also spread throughout the body.

A new oncolytic virus called RP1 (also known as vusolimogene oderparepvec) is currently being tested in a multi-center, international Phase 3 clinical trial called IGNYTE-3. Study sponsor, Replimune, has a pipeline of oncolytic viral therapies trained on addressing pressing unmet medical needs. These therapies involve direct injection of the oncolytic viral therapies into the tumor, stimulating local tumor destruction and consequently a powerful immune response with the possibility of trafficking these immune cells to destroy tumors that have spread to distant sites in the body. Furthermore, intratumoral injection of the virus may mitigate many of the adverse effects that are connected to systemic dosing. To learn more about RP1 and this clinical trial, we talked to two of the study's principal investigators: Omid Hamid, MD, Co-Director of the Melanoma Center and Phase I Immuno-Oncology Program at The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate (Los Angeles, CA) and Tawnya Bowles, MD, Surgical Oncologist and Senior Medical Director of Oncology at Intermountain Health (Salt Lake City, UT).

What is an Oncolytic Virus?

An oncolytic virus is a type of cancer treatment in which a virus infects and kills cancer cells. Oncolytic viruses are engineered to only infect cancer cells and not healthy cells. They kill cancer cells in two ways.

- First, the virus enters cancer cells and causes them to break apart and die.
- Second, the fragments created when the cancer cells die activate the immune system to be able to kill other cancer cells throughout the patient's body.

How Are New Treatments for Melanoma Tested?

New treatment options are first tested in clinical trials, which are research studies that involve human volunteers. All treatments and medications currently approved by the FDA and now available to melanoma patients were first evaluated in clinical trials for their effectiveness to treat melanoma.

Clinical trials have advantages such as possible access to promising new treatments that are not available to everyone and extra monitoring of the patient's health while on the trial. Clinical trials also have some risks such as the possibility of side effects or the treatment not working. When making treatment decisions, patients should consider all their treatment options, including discussing with their physician the potential of enrolling in a suitable clinical trial.

The IGNYTE-3 Clinical Trial Testing RP1

Replimune's IGNYTE-3 trial is currently enrolling patients in a Phase 3 clinical study testing their oncolytic virus immunotherapy, RP1, in combination with the anti-PD-1 immunotherapeutic, nivolumab, vs. standard therapies in patients who have progressed post initial therapy. The goal of IGNYTE-3 is to determine whether this treatment increases overall survival (how long a patient lives after starting treatment) in patients receiving the RP1 combination compared to patients receiving the physician selected standard treatment. This clinical trial is for patients with Stage 3 unresectable and Stage 4 metastatic melanoma whose disease progressed on anti-PD-1 and anti-CTLA-4 immunotherapy administered as a combination or in sequence. In addition, patients who have a confirmed BRAF V600 mutation should have also received some type of BRAF-directed therapy if they were medically eligible to receive this type of treatment.

The oncolytic virus being tested in the IGNYTE-3 trial is called RP1, which is a Herpes Simplex Type 1 cold sore virus genetically modified to theoretically preferentially infect tumor cells alone and

maximize tumor destruction, and at the same time, designed to activate the immune system to kill cancer cells. Following injection directly into the tumor, RP1 infects tumor cells and causes them to burst and die, which induces inflammation and immune cell trafficking to tumor. Dr. Bowles explained that RP1 is engineered differently than T-VEC because it produces two factors to more strongly activate the immune response. T-VEC produces only one of these factors.

After the consent and screening period, eligible patients are randomly assigned to one of two distinct groups:

- Group 1: RP1 (injected into the tumor every 2 weeks for a total of 8 times) plus nivolumab (Opdivo), an anti-PD1 immunotherapy (~20 infusions)

- Group 2: Physician's choice of approved standard treatment, which will be one of the following:
  - Nivolumab alone (Opdivo)
  - Nivolumab plus relatlimab (Opdualag)
  - Pembrolizumab alone (Keytruda)
  - One of the following chemotherapy medications: dacarbazine, temozolomide, or paclitaxel/albumin-bound paclitaxel

What Previous Results Led to opening the IGNYTE-3 Trial?

This Phase 3 trial is based on promising results from the Phase 1/2 IGNYTE study (NCT03767348) testing RP1 combined with nivolumab in patients who had progressed on anti-PD-1 therapy. Data presented at the European Society for Medical Oncology 2024 Congress showed that about one-third of patients' tumors responded (by shrinking) to RP1 plus nivolumab and that response to this treatment is both fast-acting and long-lasting (median duration of response from treatment initiation was 27.6 months). In addition to killing cancer cells in the injected tumor, RP1 activates the immune system so that the majority of responding patients have shrinkage in un-injected tumors that have spread to other places in the body (abscopal effect).

Results also show that the treatment was relatively safe and tolerable. The most common side effects included chills, tiredness, fever, and nausea. These side effects were minimal, not severe, and manageable.

Dr. Hamid explained that RP1 plus nivolumab works across different subgroups of patients regardless of the status of various tumor biomarkers such as PD-L1 or BRAF. Furthermore, the overall response rate (defined as either complete disappearance of tumor or partial tumor shrinkage) was 35.9% in patients with primary resistance to prior anti-PD-1 treatment and 27.7%

in patients who either didn't respond or progressed through a combination of anti-PD1 and anti-CTLA4 therapy, demonstrating the ability of the RP1 combination to overcome resistance, at least in some patients. The one-, two- and three-year survival rates were 75.3%, 63.3% and 54.8% respectively, indicating the potential for clinical benefit.

"Most remarkable was the ability of RP1 combination therapy to induce shrinkage and response in uninjected tumors locally and distant, including in uninjected visceral lesions," explained Dr. Hamid.

What are the Advantages and Disadvantages of RP1?

Dr. Hamid explained some advantages and disadvantages of RP1 compared to other approved treatments. One advantage is that unlike T-VEC, which is only injected into tumors or lymph nodes on or under the skin, RP1 can be repeatedly injected into tumors in internal organs such as the liver or lung, and patients tolerate this well. Patients with melanoma that has spread to the liver generally have a poor prognosis and few treatment options, so RP1 therapy may become an important option for treatment of these advanced melanoma patients. Unlike tumor-infiltrating lymphocyte (TIL) therapy, which was FDA approved earlier this year, RP1 can be administered to patients in the clinic quickly, does not require hospitalization, and has less severe side effects. One limitation, however, is that physicians who may be likely to inject tumors in internal organs, such as interventional radiologists or other injection specialists, must be educated on the volume of drug to be injected and how to identify suitable internal tumors that can be injected with this drug. Skin lesions are relatively easy to inject, but physicians must take special care when injecting RP1 into internal organs to avoid injury to the organ.

Dr. Hamid would like patients to know that, "this trial is available now in multiple locations in the U.S. with future plans to be opened in other countries. Patients should also know that those who are randomized to the non-RP1 arm will receive an effective second-line treatment option." Dr. Bowles stated that, "for patients concerned about whether the injections are painful, RP1 is very well tolerated, with pain levels reported to be similar to undergoing a skin biopsy with a numbing agent."

Dr. Hamid noted, "we don't stop trying to improve treatments for patients, especially those with disease resistant to current approved therapies. We are trying through the IGNYTE-3 trial to understand if this treatment will help advanced melanoma patients have longer and better lives." In addressing future research needs, both Dr. Hamid and Dr. Bowles explained that an active area of investigation is to identify biomarkers that can predict which patients will or will not respond to RP1 treatment.

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http://beta.docker.cancerhealth.com/blog/ignyte3-trial-harnessing-power-viruses-activate-immune-system-treat-advanced-melanoma