Clinical Trials to Watch: Turning Cold Tumors Hot

Researchers are using multiple strategies to tackle the same problem—how to activate T cells in people who don't respond to immunotherapy.

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Currently approved immunotherapy treatments work wonders for treating about half of stage 4 melanoma patients, a true game-changer compared to treatments that were available a decade ago. But what about the other half of patients who do not respond? What research is being conducted to improve the effectiveness of immunotherapy to benefit even more patients?

Researchers, many funded by MRA, now understand that tumors that respond to immunotherapy have lots of T cells, a cell type of the immune system, located next to and inside them. Immunotherapy treatments currently approved — ipilimumab, nivolumab, and pembrolizumab — work by taking the brakes off of T cells, letting them attack and kill the melanoma tumor.

Researchers have identified multiple reasons why some tumors don't respond to immunotherapy. They fall into four main groups: 1) T cells can't 'see' the tumor; 2) T cells cannot be turned 'on'; 3) T cells can't get inside of a tumor; and 4) other cells surrounding the tumor suppress the anti-tumor T cell response. Researchers are pursuing many strategies to overcome these mechanisms of resistance, some of which are currently being tested in patients.

Multiple approaches for flipping the 'on' switch for T cells

If you remember back to your high school biology class, T cells serve as the immune system's attack dog. Killer T-cells attack and destroy material that looks out of place — viruses, bacteria, and in some cases, cancer cells. For this to happen, T cells have to be turned on — what researchers call 'activated.' Dendritic cells — another type of cell in our immune system — swirl around our body looking for molecular 'red flags' that alert them that something is amiss; in this case, the growth of a tumor. Once dendritic cells detect a red flag — they call in the reinforcements in the form of killer T cells. If the dendritic cells fail to detect the red flag, they won't call in reinforcements, and the T cells won't attack the tumor cells.

In the past few years, several therapies designed to boost T cell activation, either by acting directly on T cells themselves or by enhancing the ability of dendritic cells to alert T cells that

something is amiss, have received Fast Track designation by the Food and Drug Administration and are being tested in melanoma patients. A Fast Track designation can only be granted to investigational drugs that treat a serious or life-threatening condition, or that fill an unmet clinical need, and that show some advantage over available treatments. These drugs will receive an expedited review by the FDA.

IMO-2125

One drug to receive this designation is Idera Pharmaceutical's experimental therapy IMO-2125. IMO-2125 works by activating a molecule called TLR9 (toll like receptor 9), which is expressed on dendritic cells. TLR9 is an important part of dendritic cells that actually detects the molecular 'red flag' before activating or 'turning on' the killer T cells. In a phase 1-2 study, investigators are testing the effectiveness of injecting IMO-225 directly into tumors in combination with the FDA-approved immunotherapy ipilimumab in patients whose melanoma progressed with either nivolumab or pembrolizumab (anti-PD1 therapy). Investigators report an overall response rate of 38% - remarkably high considering that these patients have already progressed on front-line immunotherapy.

Supporting studies demonstrate that the combination of ipilimumab and IMO-2125 revives the immune response in the patients who respond to the therapy. In addition, in these patients, both injected and uninjected lesions responded. The combination of IMO-2125 and ipilimumab is now being tested in a randomized phase 3 trial (NCT03445533) that will compare the combination against ipilimumab alone, again in melanoma patients who have failed anti-PD1 immunotherapy.

TAVO

TAVO is an experimental therapy from Oncosec that also recently received Fast Track designation. TAVO is also delivered directly into tumors by injection. It consists of DNA that makes a protein called IL-12 that activates or 'turns on' T cells. Unlike the previous study however, TAVO is also paired with a short sequence of electrical pulses that helps it enter tumors and their surrounding cells. Researchers believe that this will help TAVO more effectively activate T cells.

Initial data from a phase 2 trial (NCT03132675) of TAVO combined with pembrolizumab in melanoma patients whose tumors had advanced on anti-PD-1 therapy showed a 22.2% best overall response rate. Supporting studies suggest that the therapy helped to 'recruit' T cells directly to the tumors and generated a robust anti-tumor T cell response. This phase 2 trial is ongoing.

LN-144

Iovance Biotherapeutics' LN-144 takes an entirely different approach to activate killer T cells. LN-144, which received FDA Fast Track designation in 2017, is a cellular therapy that uses a patient's own T cells. First, T cells located within tumors (known as TILs, short for tumor-infiltrating lymphocytes) are extracted from patients and then multiplied billions of times in the lab. Then, the multiplied TILs are re-infused back into the same patient. Data from a phase 2 trial testing this approach in heavily pretreated patients with metastatic melanoma showed an objective response

rate of 56%. For patients that responded, their responses were durable. LN-144 is currently being tested in a phase 2 trial (NCT02360579) in patients with metastatic melanoma who have received at least one prior treatment with systemic therapy, including an immune checkpoint inhibitor.

IMCgp100

Patients with a rare subtype of melanoma that affects the eye, called ocular or uveal melanoma, are far less likely to respond to checkpoint immunotherapy than people with cutaneous melanoma. Immunocore's IMCgp100 is an experimental therapy currently in Phase 2 testing for uveal melanoma (NCT03070392). It also earned Fast Track designation in April, 2019.

Because uveal melanomas typically contain far fewer mutations than cells in cutaneous melanoma, killer T cells tend to be less responsive and fewer in number among uveal melanoma patients. IMCgp100 is designed to boost overall T cell responses by essentially forming a bridge between T cells and tumors. One end of the drug is designed to bind to the tumor while the other end binds directly to a T cell. When linked, the drug signals the T cells to kill the tumor. Phase 1/2 study results in a small group of patients with metastatic uveal melanoma showed an overall one year survival rate of 74%, which compares favorably with the historical rate of 43%.

Early clinical data from these four experimental approaches show great promise and illustrate the multiple strategies researchers are using to tackle the same problem — how to activate T cells in patients who do not respond to immunotherapy. Now comes the hard part — waiting for these trials to conclude to see whether any of these new approaches will help more patients benefit from immunotherapy.

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