From immunotherapy to mRNA vaccines—the latest science on melanoma treatment explained

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More than 16,000 Australians will be diagnosed with melanoma each year. Most of these will be caught early, and can be cured by surgery.

However, for patients with advanced or metastatic melanoma, which has spread from the skin to other organs, the outlook was bleak until the advent of targeted therapies (that attack specific cancer traits) and immune therapies (that leverage the immune system). Over the past decade, these treatments have seen a significant climb in the number of advanced melanoma patients surviving for at least five years after diagnosis, from less than 10% in 2011 to around 50% in 2021.

While this is great news, there are still many melanoma patients who cannot be treated effectively with current therapies. Researchers have developed two exciting new therapies that are being evaluated in clinical trials for advanced melanoma patients. Both involve the use of immunotherapy at different times and in different ways.

The first results from these trials are now being shared publicly, offering insight into the future of melanoma treatment.

Immunotherapy before surgery

Immunotherapy works by boosting the power of a patient's immune system to help kill cancer cells. One type of immunotherapy uses something called "immune checkpoint inhibitors."

Immune cells carry "immune checkpoint" proteins, which control their activity. Cancer cells can interact with these checkpoints to turn off immune cells and hide from the immune system. Immune checkpoint inhibitors block this interaction and help keep the immune system activated to fight the cancer.

Results from an ongoing phase 3 trial using immune checkpoint inhibitors were recently published in the *New England Journal of Medicine*.

This trial used two types of immune checkpoint inhibitors: nivolumab, which blocks an immune checkpoint called PD-1, and ipilimumab, which blocks CTLA-4.

Some 423 patients (including many from Australia) were enrolled in the trial, and participants were randomly assigned to one of two groups.

The first group had surgery to remove their melanoma, and were then given immunotherapy (nivolumab) to help kill any remaining cancer cells. Giving a systemic (whole body) therapy such as immunotherapy after surgery is a standard way of treating melanoma. The second group received immunotherapy first (nivolumab plus ipilimumab) and then underwent surgery. This is a new approach to treating these cancers.

Based on previous observations, the researchers had predicted that giving patients immunotherapy while the whole tumor was still present would activate the tumor-fighting abilities of the patient's immune system much better than giving it once the tumor had been removed.

Sure enough, 12 months after starting therapy, 83.7% of patients who received immunotherapy before surgery remained cancer-free, compared to 57.2% in the control group who received immunotherapy after surgery.

Based on these results, Australian of the year Georgina Long—who co-led the trial with Christian Blank from The Netherlands Cancer Institute—has suggested this method of immunotherapy before surgery should be considered a new standard of treatment for higher risk stage 3 melanoma. She also said a similar strategy should be evaluated for other

cancers.

The promising results of this phase 3 trial suggest we might see this combination treatment being used in Australian hospitals within the next few years.

mRNA vaccines

Another emerging form of melanoma therapy is the post-surgery combination of a different checkpoint inhibitor (pembrolizumab, which blocks PD-1), with a messenger RNA vaccine (mRNA-4157).

While checkpoint inhibitors like pembrolizumab have been around for more than a decade, mRNA vaccines like mRNA-4157 are a newer phenomenon. You might be familiar with mRNA vaccines though, as the biotechnology companies Pfizer-BioNTech and Moderna released COVID vaccines based on mRNA technology.

mRNA-4157 works basically the same way—the mRNA is injected into the patient and produces antigens, which are small proteins that train the body's immune system to attack a disease (in this case, cancer, and for COVID, the virus).

However, mRNA-4157 is unique—literally. It's a type of personalized medicine, where the mRNA is created specifically to match a patient's cancer. First, the patient's tumor is genetically sequenced to figure out what antigens will best help the immune system to recognize their cancer. Then a patient-specific version of mRNA-4157 is created that produces those antigens.

The latest results of a three-year, phase 2 clinical trial which combined pembrolizumab and mRNA-4157 were announced this past week. Overall, 2.5 years after starting the trial, 74.8% of patients treated with

immunotherapy combined with mRNA-4157 post-surgery remained cancer-free, compared to 55.6% of those treated with immunotherapy alone. These were patients who were suffering from high-risk, late-stage forms of melanoma, who generally have poor outcomes.

It's worth noting these results have not yet been published in peer-reviewed journals. They're available as company announcements, and were also presented at some cancer conferences in the United States.

Based on the results of this trial, the combination of pembrolizumab and the vaccine progressed to a phase 3 trial in 2023, with the first patients being enrolled in Australia. But the final results of this trial are not expected until 2029.

It is hoped this mRNA-based anti-cancer vaccine will blaze a trail for vaccines targeting other types of cancer, not just melanoma, particularly in combination with checkpoint inhibitors to help stimulate the immune system.

Despite these ongoing advances in melanoma treatment, the best way to fight cancer is still prevention which, in the case of melanoma, means protecting yourself from UV exposure wherever possible.

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