Drug combination for stage IV melanoma shows success in trial

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Melanoma. Credit: Wikimedia Commons/National Cancer Institute

A new multidrug treatment for patients with stage IV melanoma has proven effective after a three-year clinical trial at the University of Colorado Cancer Center.

The study, which was designed and led by CU Cancer Center members,

was aimed at overcoming the immune suppression that occurs in some patients with metastatic melanoma—skin cancer that has spread to organs like the lungs.

"We know immunotherapy is effective for many melanoma patients, but it doesn't work for everybody. Sometimes the tumors suppress the immune system and prevent the immune reaction," says CU Cancer Center member Martin McCarter, MD, who led the clinical trial.

"We are very interested in trying to overcome this immune suppression, and by studying our melanoma patients at the cancer center we identified a particular cell population, called myeloid-derived suppressor cells, that plays a role in melanoma-induced immunosuppression."

The drug trial was designed to specifically target myeloid-derived suppressor cells and determine if that could improve immune responses to standard therapy.

One-two punch

The CU study examined the combination of the common immunotherapy drug pembrolizumab (Keytruda) with all-trans retinoic acid (ATRA), a chemotherapy drug that targets myeloid-derived suppressor cells. In results just published in the journal *Clinical Cancer Research*, the CU researchers found that the drug combination is effective, with an overall response rate of 71%. Fifty percent of patients experienced a complete response, and the one-year overall survival rate was 80%.

"For comparison purposes, pembrolizumab alone in this patient population achieves around a 40% response rate," says McCarter, professor of surgical oncology at the University of Colorado School of Medicine. "Combining that with ATRA and getting to a 71% response

rate—that's potentially a huge advance. That is as good as you see with the best combination immunotherapy regimens out there."

The good news about the pembrolizumab-ATRA combination is that it does not contribute to increased toxicity, he says. The most common side effect is a headache that goes away once the treatment is complete. The results of the study are very promising for metastatic melanoma patients who currently don't have many options if traditional immunotherapy is not successful in treating their cancer.

Further study begins

The CU-discovered drug combination will now be rolled out to a larger population as Merck, the pharmaceutical company that manufactures pembrolizumab, is expanding the clinical trial to a wider patient population as part of its "umbrella program."

"Merck has contracted with several high-volume melanoma centers across the world, and any time they get a new combo drug that looks potentially promising, they can open it right away at all the centers," McCarter says. "So they took this combo and opened it in their multicenter program, and it enrolled so fast that trial enrollment closed in under a month. What that says is there is desperate need for these new treatments."

The wider Merck trial is testing the pembrolizumab-ATRA combination in patients who have already failed other types of immunotherapies, making for a tougher hurdle than the CU trial that employed the combination as a first-line treatment.

"We showed it was safe and effective, so it makes sense to move it in that direction," McCarter says. "That's really the patient group that needs the most help right now. If the tumor doesn't respond to immunotherapy,

the chances of responding to anything after that are very small. We're trying to find ways to manipulate the tumor microenvironment to allow a better immune response."

Results worth celebrating

While the CU researchers await the results of the Merck study, they are celebrating the response rates of their initial trial, which were much higher than expected.

"From the outset, we felt like if these trial results were equal to what was out there already, in terms of the response just to pembrolizumab, but we were successful in targeting the myeloid-derived suppressor cells, that would have been a victory," McCarter says. "But we got more than that, and the clinical response seemed better than expected.

"You dream about this kind of thing. You work so hard on the science, but just like in the startup business world, 95% of these things fail," McCarter adds. "Despite all your best intentions or all the best science that looks like, 'This should work,' when you move it into humans, it often doesn't work. So to see this hypothetical mechanism actually work and see it translate into actually helping patients? That's why we're in this business."

More information: Richard P. Tobin et al, Targeting MDSC Differentiation Using ATRA: A Phase I/II Clinical Trial Combining Pembrolizumab and All-Trans Retinoic Acid for Metastatic Melanoma, *Clinical Cancer Research* (2022). DOI: 10.1158/1078-0432.CCR-22-2495

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