New Therapy May Reverse Resistance to Keytruda for Melanoma

TLR9 agonist restores response to immunotherapy in people with advanced melanoma.

May 7, 2018 By Liz Highleyman

A new type of therapy can turn “cold” melanoma tumors that don’t respond well to immunotherapy into “hot” tumors that are susceptible to the checkpoint inhibitor Keytruda (pembrolizumab), according to an early study presented at the recent American Association for Cancer Research (AACR) annual meeting.

Results from a Phase Ib trial showed that CMP-001, a toll-like receptor 9 (TLR9) agonist that turns on interferon gene expression, appears to stimulate immune responses and reverse resistance to Keytruda in people with metastatic melanoma, lead investigator Mohammed Milhem, MBBS, of the University of Iowa reported.

Melanoma typically starts as a skin cancer, but it can spread to other parts of the body, a process known as metastasis. If it is not caught early, it often invades the lungs, liver, bones and brain.

Keytruda blocks PD-1, a receptor on T cells that plays a role in regulating immune function. Some tumors can use PD-1 to turn off immune responses against them, and drugs that block PD-1 can release the brakes and restore T-cell activity. Compared with other types of cancer, melanoma typically has many mutations, which makes it easier for T cells to recognize and attack. Keytruda is currently approved for the people with inoperable or metastatic melanoma, but more than half of them eventually develop resistance to the drug.

“Checkpoint inhibition is quickly becoming a key tool for oncologists to treat cancer. However, there are many patients that either initially respond to checkpoint inhibition and then progress, or never respond to this therapy to begin with,” Milhem said in an AACR press release. “Finding safe and effective therapies for these patients is critical.”

Tumors with increased interferon gene expression are more responsive to PD-1 inhibition, leading researchers to test a combination of Keytruda plus a drug that promotes interferon expression. CMP-001 is designed to activate tumor-associated dendritic cells via TLR9 receptors, leading to an interferon-rich tumor microenvironment that promotes CD8 T cell responses.

“The strongest known inducer of interferon production is the TLR9 pathway, so we thought that

adding a TLR9 activator to anti-PD-1 therapy would elicit a response in patients who stopped or never responded to PD-1 inhibition," Milhem explained.

This study included 85 people with advanced melanoma who either did not respond to or progressed while taking a PD-1 inhibitor. Of these, 44 were enrolled in a dose-escalation phase to determine the best balance of activity and tolerability. They received injections of CMP-001 directly into accessible tumors at doses ranging from 1 to 10 milligrams in combination with standard doses of Keytruda.

Treatment was given once weekly for either seven or two weeks, followed by dosing every three weeks until discontinuation due to disease progression or toxicity. In addition, 41 people were enrolled in an ongoing expansion phase using a 5 mg once-weekly dose.

At the time of this interim analysis, 18 people had responded, including two complete responses. The overall objective response rate, meaning complete or partial tumor shrinkage, was 22 percent (23 percent for those who received weekly dosing for seven weeks and 15 percent for those who switched to less frequent dosing after two weeks).

Thirteen of the responders remain in the study; most have maintained responses for more than six months and some did so for more than a year. Three other participants initially experienced disease progression but later responded. Some people showed ongoing responses after stopping treatment. The median duration of response has not yet been reached.

The researchers saw a reduction not only in the tumors injected with CMP-001, but also in other tumors that had spread to the lymph nodes, liver or spleen, suggesting that T cells activated by Keytruda were working throughout the body, known as an abscopal effect. Tumor biopsies revealed an increase in tumor-infiltrating T cells, increased expression of PD-L1 (the ligand, or binding partner of PD-1) and greater inflammation, according to the study abstract.

CMP-001 appeared to be generally safe and well tolerated in this early study. During the dose escalation phase, there was only one dose-limiting toxicity. Checkpoint inhibitors can cause an overactive immune response that harms healthy organs and tissues as well as with cancer cells. The most common adverse events were fever, headache, nausea and vomiting, hypotension (abnormally low blood pressure) and rigors (chills and shivering).

"Additional larger studies in this patient population will need to be conducted to further evaluate the clinical benefit, but if the current results are confirmed, it appears that this combination could offer a new treatment option for patients with advanced melanoma who are not responsive to pembrolizumab," Milhem said.

He added that use of CMP-001 may make it possible for some people who have stopped Keytruda due to loss of response to successfully restart treatment.

Click here to read the AACR study abstract.

Click here to read an AACR press release about the study.

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