New Immunotherapy Drugs Targeting LAG-3 Show Great Promise

Encouraging clinical trials find new immunotherapy drugs targeting a certain protein may be effective treatments for melanoma.

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With 13 new therapies approved in the past decade, the outcomes for patients with advanced melanoma have improved tremendously. But, there are still many patients who do not benefit from these treatments, who benefit initially but then see their melanomas come back, and those who experience life-changing side effects as a result of the medications they take. For all of these reasons, new treatments options are still urgently needed.

Researchers presented a series of highly encouraging clinical trial results at the recent American Society for Clinical Oncology (ASCO) annual meeting that suggest that new drugs targeting the protein LAG-3 – developed by BMS and Regeneron – may be an important addition to the current treatment arsenal.

Like PD-1 and CTLA4, which are the targets of currently approved immunotherapies for melanoma, LAG-3 is an immune checkpoint molecule. LAG-3 often appears together with PD-1 on the surface of tumor-infiltrating lymphocytes (TILs) and contributes to T cell "exhaustion." Exhausted T cells become un-responsive and aren't able to effectively attack tumors. Studies in animal models suggested that blocking both PD-1 and LAG-3 led to better tumor killing compared to blocking either one of the proteins alone, which laid the groundwork for clinical trials testing this strategy.

Blocking PD-1 and LAG-3 in Patients with Advanced Melanoma

MRA-funded investigator Evan Lipson, of Johns Hopkins University, presented the results of the RELATIVITY-047 phase 2/3 trial that tested an experimental LAG-3-blocking therapy developed by BMS called relatlimab in combination with their FDA-approved PD-1-blocking antibody nivolumab (rela + nivo) versus nivo alone as a first line therapy in patients with advanced, unresectable melanoma (NCT03470922). After an average follow-up of 13.2 months, Lipson reported that the experimental combination of rela + nivo demonstrated a superior progression free survival (PFS) of 10.12 months compared to nivo alone (4.63 months). Interestingly, patients benefitted from rela + nivo regardless of whether their tumors expressed LAG-3 at the time of treatment initiation.

Importantly, the experimental combo was reasonably safe, with only 18.9% of patients experiencing serious side effects, what researchers call grade 3-4 treatment-related adverse

events. This is a larger percentage compared to patients receiving nivo alone (9.7%), but substantially lower than what has historically been observed for patients taking the FDA-approved combination of ipilimumab (ipi) + nivo (~50%).

Due to trial design and a pause in enrollment due to COVID-19, objective response rate and overall survival data aren't yet available. However, the available results indicate that, pending FDA approval, rela + nivo may eventually become the frontline immunotherapy combination of choice given its high efficacy and more manageable safety profile.

This is the first phase 3 study to validate inhibition of the LAG-3 immune checkpoint as a therapeutic strategy for patients with cancer," says Evan Lipson, MD. "Our findings establish the LAG-3 pathway as the third immune checkpoint pathway in history, after CTLA-4 and PD-1, for which blockade has clinical benefit."

Omid Hamid of the Angeles Clinic presented data on another trial testing a different LAG-3 blockade developed by Regeneron, in combination with Regeneron's PD-1 inhibitor (NCT03005782). In this phase 1 trial, fianlimab (targeting LAG-3) plus cemiplimab (targeting PD-1) demonstrated an overall response rate (ORR) of 66.7% in patients with advanced melanoma who had not been previously treated with PD-1/PD-L1 inhibitors and 13.3% in patients previously treated with PD-1/PD-L1. Hamid noted that serious side effects occurred in 39.6% of patients. These results further support the high clinical activity and more manageable safety profile of combination PD-1/LAG-3 blockade.

"Responses seen were rapid, deep, and durable and seen in high-risk populations," says Omid Hamid, MD. "Fianlimab + cemiplimab combination produced clinical activity for patients with advanced melanoma similar to anti–PD-1 + CTLA-4 combination therapy, but with lower demonstrated rates of adverse events."

Combination LAG-3 + PD-1 Blockade in Patients with Earlier Stage Melanoma

Researchers are also studying whether therapies used for advanced melanoma are effective in patients with earlier stage disease and if they can help prevent tumor recurrence. One promising approach, called neoadjuvant therapy, is to treat patients with a systemic therapy, such as a PD-1-blocking antibody, or combination ipi + nivo, for several weeks prior to surgery to remove the tumor. Following surgery, patients often continue to receive systemic therapy to ensure their tumors do not return, what is called adjuvant therapy.

MRA-funded investigator Rodabe Amaria, of University of Texas MD Anderson Cancer Center, reported results from a trial testing neoadjuvant rela + nivo followed by adjuvant nivo in patients with stage 3 or 4 melanoma that can be surgically removed. Dr. Amaria observed a major pathological response rate (MPR, thought to be a surrogate marker for treatment effectiveness) in 66% of patients and a 57% overall radiographic response rate (does it look like it grew or shrunk in scans) . At an average follow up of 16.2 months, no patients who had experienced an MPR had their cancer recur whereas ~30% of patients who did not have a major pathological response experienced a recurrence. Overall, rela + nivo was well tolerated in the neoadjuvant setting, with

26% of patients experiencing a serious side effect.

“Neoadjuvant nivo + rela looks equally effective as ipi + nivo in the neoadjuvant setting but with lower toxicity,” says Rodabe Amaria, MD. “This makes this an attractive regimen for further use because any treatment that is efficacious and non-toxic is the ultimate dream for both patients and providers.”

Together, these trials point to therapies targeting LAG-3 in combination with PD-1 as an important addition to the melanoma treatment landscape that will improve outcomes for melanoma patients.

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