Personalized vaccine therapy targets metastatic melanoma.

by Cliff Dominy PhD

Pharmaceutical giant Merck (NYSE: MRK) and biotechnology leader Moderna (NASD: MRNA) have embarked on a groundbreaking Phase 3 clinical trial to evaluate the combined efficacy of their innovative treatments for metastatic melanoma.

Early results from Phase 2 studies have shown promising improvements in survival outcomes for patients with stage 4 metastatic melanoma[1]. The approach combines Merck's FDA-approved checkpoint inhibitor, KEYTRUDA, with Moderna's mRNA-4157 tumor-targeting mRNA vaccine technology.

Metastatic melanoma is an aggressive epidermal cancer which can metastasize, forming secondary tumours elsewhere in the body. The five year survival rate is just 35%. Pharma giant Merck had already shown that immunotherapy with just KEYTRUDA, could improve the patients' five year survival rate to 50% [2]. The FDA approved the drug in 2014 for the treatment of resectable melanoma.

In 2019, Merck partnered with Moderna, to see if mRNA-biotech's new individualized vaccine technology, in conjunction with their established delivery platform, could further improve outcomes for patients with the disease. Modernas mRNA technology had already garnered worldwide attention during the recent pandemic for the safety and efficacy of their COVID-19 vaccine, SpikeVax™.

Moderna's mRNA-4157 is a mRNA cancer vaccine which can be customized to mimic tumour-specific antigens expressed by a patient with melanoma. These so called neoantigens are specific to a particular tumour and can be identified after biopsy. mRNA encoding the patient-specific neoantigens are synthesized to produce a personalized vaccine. The vaccine is injected into the site of the resected tumour where it is taken up and expressed by the target cells to produce tumour antigens.

However, the vaccine might need a little help with alerting the immune system to its presence. Melanoma tumours have the ability to hide undetected in the body. It's how they grow. KEYTRUDA, the second drug in the combination, functions by unmasking the tumour and exposing it, along with the introduced synthetic mRNA, to immune surveillance. The body's innate immune system can now identify the tumour and remove it.

The initial results of the collaboration, a phase 2 trial, were published in early 2024 [1] It compared the mRNA-4157/KEYTRUDA combination (n=107) against KEYTRUDA therapy alone (n=50). Phase 2 results showed that the combination therapy arm had a 79% eighteen month tumour-free remission rate versus 62% in the KEYTRUDA arm alone. Note, this was the remission rate - not the survival rate. It was enough for the FDA to fast-track the phase 3 trial application process.

Adverse events to the combination therapy were generally mild and similar in each arm (36%). This suggests that the mRNA component of the therapy did not alter the safety profile of the original KEYTRUDA protocol.

The phase 3 trial is using the same promising approach. The new trial, named V940-001, is a fully randomised, double-blind controlled study, designed to evaluate the safety and efficacy of the therapy in a much larger population. The primary objective of the trial is the five year tumour-free remission rate, with the secondary objective being the five year survival rate.

V940-001 aims to enroll 1089 patients at 165 sites worldwide. Adults diagnosed with stage 2B - 4 metastatic melanoma are eligible to participate. The primary tumour should have been surgically removed within thirteen weeks of enrolment with no evidence of secondary tumour progression. Given the much longer duration of the V940-001 trial, phase 3 results are expected in 2029.

Research, as they say, is ongoing - and like with any other trial there are no guarantees. However given the promising phase 2 results, expectations remain high.

Combination therapies are becoming more common in the clinical trial space. Using different combinations of established drugs like KEYTRUDA and innovative personalized therapies, a new range of potentially effective therapies are giving clinicians options in the fight against metastatic melanoma.

References

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