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Revolutionizing Cancer Treatment: mRNA-Based Personalized Cancer Vaccine Shows Promise in Melanoma Therapy

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Melanoma is considered the most dangerous type of skin cancer due to its potential to spread quickly to other parts of the body. Unfortunately, the incidence of melanoma has been on the rise in recent decades, and it is estimated that there were approximately 325,000 new cases worldwide and 57,000 deaths due to melanoma in 2020 (*JAMA Dermatol* 2022;158:495-503). In the United States, skin cancer is one of the most frequently diagnosed forms of cancer, and melanoma is responsible for the majority of skin cancer-related deaths. Shockingly, nearly 8,000 people were estimated to die from melanoma in the U.S. in 2022, while almost 100,000 new cases were projected to be diagnosed (asamonitor.pub/3LNJNfu). The five-year survival rates for stage III melanoma are estimated to be 60.3%,

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Neuromuscular Monitoring: What's New and Where Are We Headed?

Patrick Forrest, MD **Wiebke Ackermann, MD** **Abbas Al-Qamari, MD**

Many readers may now be familiar with the new ASA practice guidelines for monitoring and antagonism of neuromuscular blockade that were published this past January (*Anesthesiology* 2023;138:13-41). For those who are not, this article may serve as a brief overview of the advances made in neuromuscular monitoring in recent

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My Top 5 List of Impactful Health Care Trends

Paul Pomerantz, FACHE

It is daunting to reflect on the fact that I have just a few quarterly columns left. In this one, I will share my observations on the major trends impacting the specialty and the society. In October, I will reflect on the major milestones of the last decade.

"The future ain't what it used to be" – Yogi Berra

Years back, when I was first getting my start as a hospital administrator, I was told that the future was managed care, that fee-for-service would be a thing of the past. That prediction has largely not been realized. On the other hand, I was employed in a health system that was working to accumulate market share through the acquisition of primary care physician practices and to ensure future viability through preferred provider arrangements with health plans. I feel that we were early adopters of the trend toward vertical integration. Philadelphia was then home to six medical schools and

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PERIODICALS

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while they drop to just 16.2% for stage IV (asamonitor.pub/3nkfwLX).

Patients with cancer often require surgery, and their treatment plans may include chemotherapy, radiation therapy, and immunotherapy, among other interventions. Therefore, understanding the available treatment options can help provide better care for patients undergoing cancer surgery.

"Anesthesiologists need to be familiar with the potential changes in medication management for patients receiving the new vaccine type and adjust the anesthetic plan accordingly. They must also work with the oncology team to understand the patient's cancer type and planned treatment regimen for preoperative evaluation."

In the past 25 years, vaccine strategies for treating cancer aimed to stimulate immune responses against tumor-associated antigens that are not entirely specific to the tumor. However, more recent cancer vaccine approaches have focused on targeting neoantigens, which are unique to individual tumor mutations, making them specific to cancer cells (*Signal Transduct Target Ther* 2023;8:9). This approach has gained attention in the treatment of melanoma, where immunotherapy has become a standard method. Although immunotherapy has shown success in treating melanoma, it does not work for all patients, as melanoma cells have the ability to evade the immune system and become resistant to treatment (*J Immunol Res* 2020;2020:9235638). For this reason, researchers have explored the addition of vaccines. While vaccines are primarily used for preventing infections, they can also be customized to target proteins involved in cancer.

In a new study, Moderna Inc. and Merck have released promising results from their joint clinical trial, which investigated the combination of an investigational individualized neoantigen therapy (INT), mRNA-4157 (V940), with Merck's anti-programmed death receptor-1 (PD-1) therapy, pembrolizumab, for the treatment of high-risk melanoma. The findings of the open-label, randomized, phase 2b mRNA-4157-P201/KEYNOTE-942 trial (asamonitor.pub/44kIk7H) were presented at the American Association for Cancer Research Annual Meeting 2023 (asamonitor.pub/3VxmppN).

mRNA-4157/V940

mRNA-4157/V940 is a personalized mRNA-based cancer vaccine that encodes up to 34 patient-specific tumor neoantigens. Similar to the COVID-19 vaccine, mRNA-4157/V940 is based on messenger RNA and designed to teach the body's immune system to recognize cancer cells as different from normal cells. This novel vaccine stimulates an immune response by generating specific T cell responses based on the unique mutational signature of a patient's tumor. Individualized INTs, like mRNA-4157/V940, prime the immune system to generate a tailored antitumor response that is specific to a patient's tumor mutation signature. It is administered by injection, and its neoantigen sequences undergo natural cellular antigen processing and presentation.

Pembrolizumab injection

Pembrolizumab is an immunotherapy that enhances the body's ability to detect and fight tumor cells. The therapy functions as an anti-PD-1 agent by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2. By doing so, pembrolizumab activates T lymphocytes, which may affect both tumor cells and healthy cells. Early clinical studies suggest that combining pembrolizumab with mRNA-4157/V940 may enhance T cell-mediated destruction of tumor cells.

KEYNOTE-942/mRNA-4157-P201 study results

In the current randomized phase 2b trial, researchers at NYU Langone Health and its Perlmutter Cancer Center investigated the efficacy of mRNA-4157/V940 in combination with pembrolizumab, the standard-of-care adjuvant therapy, in patients with resected stages IIIB/IIIC/IIID and IV melanoma. The ongoing trial enrolled 157 patients who had undergone surgery to remove melanoma from lymph nodes or other organs, and were at high risk of the disease returning. Patients were randomized 2:1 to receive either mRNA-4157/V940 and pembrolizumab, or pembrolizumab alone for approximately one year until disease recurrence or unacceptable toxicity. Eligibility criteria included patients with resectable cutaneous melanoma metastatic to a lymph node, complete resection within 13 weeks prior to the first dose of pembrolizumab, and no evidence of brain metastases.

The primary endpoint of the trial is recurrence-free survival (RFS), with secondary endpoints including distant metastasis-free survival and safety. Exploratory endpoints of the study include analyzing the distribution of tumor mutational burden (TMB) expression in baseline tumor samples among the study groups and assessing its correlation with the primary RFS endpoint.

A total of 107 patients received mRNA-4157 (V940) in combination with pembrolizumab, and 50 patients were treated with pembrolizumab alone. The findings revealed that adjuvant treatment with mRNA-4157 (V940) in combination with pembrolizumab reduced the risk of recurrence or death by 44% compared to pembrolizumab alone.

After two years of follow-up, the cancer returned in 24 subjects (22.4%) in the combination arm, compared with 20 out of 50 (40%) in the control arm. The combination arm had a 12-month RFS rate of 83.4% (95% CI, 74.7-89.3), while the control arm had a rate of 77.1% (95% CI, 62.5-86.6). The 18-month RFS rate was 78.6% (95% CI, 69.0-85.6) in the combination arm and 62.2% (95% CI, 46.9-74.3) in the control arm. The RFS benefit with the combination was observed in tumors with high and low tumor inflammation score and with positive and negative PD-L1 expression.

The researchers also conducted a subgroup analysis to assess the efficacy of mRNA-4157 (V940) in combination with pembrolizumab based on the TMB status of patients. TMB refers to the number of mutations in a tumor's DNA, which may be linked to response to treatment. The analysis found that the vaccine-pembrolizumab combination reduced the risk of recurrence or death by 35% in patients with high TMB (HR, 0.642; 95% CI, 0.284-1.494) and 41% in those with low TMB (HR, 0.586; 95% CI, 0.243-1.415), suggesting that the vaccine may be effective regardless of TMB. Further studies are planned to explore the association between TMB and treatment response, as well as identify potential biomarkers for better outcomes.

The combination of mRNA-4157/V940 and pembrolizumab had a similar safety profile to the individual agents alone, with serious adverse events occurring in 14.4% of patients compared to 10% for pembrolizumab alone. Fatigue was the most commonly reported side effect associated with the vaccine.

As a result of the positive outcomes, mRNA-4157/V940 combined with pembrolizumab has been granted breakthrough therapy designation by the FDA and PRIME scheme by the European Medicines Agency. The FDA has also authorized the combination for adjuvant treatment of high-risk melanoma following complete resection. Additionally, Phase 3 trials have been planned at NYU Langone and other medical centers globally to compare the effectiveness of this combination with pembrolizumab alone. Moderna and Merck are among several groups collaborating on mRNA-based cancer vaccines, such as BioNTech and Gritstone Bio.

Implications for anesthesiologists

Anesthesiologists need to be aware of the potential clinical implications of the combination treatment of mRNA-4157 and pembrolizumab. These implications include changes in treatment plans, potential side effects, patient education, tailored anesthesia management, and preoperative evaluation.

It is important for anesthesiologists to stay up to date on the latest developments in cancer treatment and work closely with the oncology team to provide the best possible care to patients undergoing surgery. Anesthesiologists need to be familiar with the potential changes in medication management for patients receiving the new vaccine type and adjust the anesthetic plan accordingly. They must also work with the oncology team to understand the patient's cancer type and planned treatment regimen for preoperative evaluation. Additionally, anesthesiologists should also be knowledgeable about the unique side effects associated with immunotherapy, including immune-related adverse events, which can affect multiple organ systems, and be prepared to manage them in the perioperative period. Lastly, they can play a critical role in educating patients about the benefits and potential risks of this treatment option on their anesthesia care and overall surgical outcomes. ■

Dibash K. Das serves as medical editor for Gastroenterology Advisor. He holds a PhD in molecular, cellular, and developmental biology from the CUNY Graduate Center and an advanced certificate in clinical and translational investigation from Weill Cornell Medicine.