MELANOMA IN FOCUS

Current Developments in Melanoma

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Are Vaccines Making a Comeback in Melanoma?

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H&O What vaccines are approved for use in melanoma?

JW We do not have any true vaccines that are approved and used for cancer at this time. Some people consider talimogene laherparepvec, or T-VEC (Imlygic, Amgen), to be a vaccine, but T-VEC is simply a therapeutic that is injected directly into tumors. Randomized clinical trials have not established any vaccine, apart from the human papillomavirus (HPV) vaccine, to be beneficial in treating any type of cancer. The HPV vaccine is approved to treat precursor conditions that lead to cervical cancer and other HPV-related cancers. Although the HPV vaccine is technically a cancer vaccine, we still do not have vaccines that successfully treat invasive malignancies in the adjuvant or metastatic setting.

H&O What types of vaccines are being investigated for use in melanoma?

JW Some researchers in the United States and Europe are still working on conducting small-scale trials with dendritic cell vaccines, which is amazing because this technology dates back to the 1990s. I used to receive funding from the National Institutes of Health to conduct trials of dendritic cell vaccines. However, most randomized controlled trials have shown little benefit from these vaccines. I think that this technology holds more interest as a discovery approach in the laboratory than as a pathway to provide clinical benefit to patients.

Approximately 20 or 25 years ago, trials of peptide vaccines in melanoma were very popular. I have administered peptide vaccines to hundreds of patients as part of clinical trials, but I am not convinced that any of these patients benefited. At the time, we were using peptides from either tumor-associated antigens (TAAs) that were overexpressed on tumor cells or cancer/testis antigens (CTAs) that were present on embryonal cells, oocytes, and other cells, and were highly overexpressed on tumors. These were all normal proteins or glycoproteins present on normal cells.

Another type of vaccine that is being investigated is nucleic acid vaccines, which include RNA vaccines. Drs Robert Schreiber, Mark Smyth, and James Allison are among the tumor immunologists who established neoantigens as the optimal target for cancer vaccines. In addition to knowing the proper target to mount an effective antitumor response, we need to have the right vehicle to ensure that the response has an adequate magnitude and duration to generate clinical benefit. Nucleic acid vaccines may be the key.

H&O What are the potential advantages of using a personalized vaccine for melanoma?

JW The holy grail of tumor immunology has always been to develop an off-the-shelf vaccine that could be used in many or most patients with a particular type of cancer, such as melanoma. The challenge is that the antigens that tumors most commonly overexpress are also expressed by

normal cells. This creates 2 problems: first, that patients have already developed a tolerance to these antigens; and second, that generating an immune response against those antigens creates off-target effects and toxicity.

The only antigens that are completely tumor-specific are neoantigens, which are generally a result of mutations. These mutations represent genetic changes, mainly single-nucleotide variants, but also fusions, insertions, or deletions in the DNA of the tumor that are expressed as RNA and then encoded as proteins that are unique to the tumor. It would be nice if driver mutations, such as those in *NRAS* or *TP53*, could also encode peptides that would be recognized by the immune system. These mutations tend to occur very early, however, and sometimes even occur in nonmalignant tissue. As long as it is present in the majority of the tumor cells, an antigen that develops late in the onset of that tumor makes a better target because the body has not developed a true tolerance to it. RNA vaccines from Pfizer/BioNTech and Moderna proved to be game-changers against COVID, and I expect RNA vaccines to be similarly valuable in cancer immunology.

H&O Could you discuss the design of your KEYNOTE-942 study?

JW KEYNOTE-942 was a randomized phase 2 study that enrolled 157 patients with completely resected, high-risk stages IIIB/C/D and IV cutaneous melanoma. Patients were randomly assigned in a 2:1 ratio to a personalized messenger RNA (mRNA) vaccine every 3 weeks for up to 9 doses plus pembrolizumab (Keytruda, Merck; n=107) every 3 weeks for up to 18 doses vs pembrolizumab alone (n=50).

I am a big fan of randomized phase 2 studies, which typically enroll around 100 to 200 patients, because cancer treatments often fail to work in phase 3 studies. I do not want to subject many hundreds of patients to potentially toxic treatments unless a phase 2 study has been conducted that points to efficacy. Unfortunately, it has become commonplace for investigators to move directly from a small phase 1/2 study of 30 or so patients to a phase 3 study that enrolls hundreds. This practice has led to some major failures in metastatic melanoma over the past 5 years. I also like studies that employ 2:1 randomization because it means that patients have a greater chance of receiving what they perceive as the "good" treatment. If the control treatment is simply what the patient would be receiving anyway, enrolling in a clinical trial becomes an especially attractive option for patients.

Moderna was the manufacturer of the mRNA-4157/V940 vaccine that we used in our trial. The study was complicated by being performed at the height of the COVID pandemic. At one point, Moderna had to stop production of the melanoma vaccine to devote all their manufacturing capabilities to the COVID vaccine. To avoid running out of the experimental treatment, we manually reassigned a small number of patients to the control arm.

The primary endpoint of this trial was recurrence-free survival (RFS). In the results presented at the most recent meetings of the American Association for Cancer Research and the American Society of Clinical Oncology, the risk of relapse after a median follow-up of approximately 2 years was 44% lower in the combination group than in the control group (hazard ratio [HR], 0.561; 95% CI, 0.309-1.017; 1-sided *P*=.0266), although the result was not statistically significant. I was not involved in the original statistical design, but it called for a 1-sided *P* value of .1. This is very modest, but it is what can be expected from a phase 2 study. In addition, 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. Again, this difference was clinically significant but not statistically significant.

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If we look at distant metastasis–free survival (DMFS), which was a secondary endpoint, the difference between the groups was statistically significant for the combination treatment vs the control treatment (HR, 0.347; 95% CI, 0.145-0.828; 1-sided *P*=.0063). Very few patients died, so no overall survival data are available.

An interesting finding is that there was a late break in the survival curve for both RFS and DMFS. The explanation is that it took approximately 6 to 7 weeks to manufacture the vaccine for the combination arm, meaning that patients in the combination arm received pembrolizumab alone until the vaccine was ready and again after the 9 doses of vaccine had been administered.

Toxicity was tolerable with the combination. The use of the vaccine produced side effects consistent with those observed with mRNA COVID vaccines, namely fatigue, fever, chills, and a sore arm, but were more pronounced. We administered alternating doses of ibuprofen

and acetaminophen to reduce these side effects. None of the 10 patients in the trial from our institution needed to stop taking the vaccine because of side effects, and we saw that side effects became successively less pronounced after the first couple of shots. In addition, the vaccine did not amplify the immune-related adverse events typically associated with pembrolizumab.

One unexpected finding was that after patients had completed their 9 vaccines and were on pembrolizumab alone, they tended to experience fewer side effects from the pembrolizumab. I suspect that the side effects of pembrolizumab also attenuated over time. We hope to have more data available by November or December of this year, and the phase 3 trial has begun enrolling patients in Australia (NCT05933577). I expect this study to be extremely popular as soon as we gain approval to begin enrolling patients in the United States and Europe. In the meantime, we can enroll patients in an extension of the phase 2 study in which we are apheresing patients to get peripheral blood samples to study in detail.

H&O Are other studies looking at the use of vaccines in melanoma?

JW A phase 1a/b study by BioNTech and Genentech, which began in 2017, is looking at the use of the neoantigen vaccine autogene cevumeran as a single agent and in combination with atezolizumab (Tecentriq, Genentech) in patients with locally advanced or metastatic tumors, including melanoma (NCT03289962). The estimated completion date for this study is November 2024.

Gritstone Bio is a third company that is developing an RNA-type vaccine. However, this one is a little different because it employs a prime-boost strategy with a chimpanzee virus. In results from a phase 1/2 trial in patients with advanced metastatic solid tumors (not melanoma) that appeared in *Nature Medicine* in 2022, the individualized vaccine regimen in combination with nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb) was shown to be safe and well tolerated, with no dose-limiting toxicities.

H&O Would you say that vaccines are making a comeback in melanoma?

JW I would say that vaccines are making a comeback in melanoma. This is saying a lot because I was a bona fide skeptic when it came to cancer vaccines based on results in the 1990s, when we were using the wrong antigens and the wrong constructs. Now, with the use of neoantigens and RNA-microencapsulated nanoparticles, I think we are on the right path. I am highly optimistic that the results of the phase 3 study of the mRNA-4157/V940 vaccine will be positive.

Disclosure

Dr Weber has consulted for Merck, Genentech, AstraZeneca, GSK, Novartis, Nektar, Celldex, Incyte, Biond, Moderna, ImCheck, Sellas, Evaxion, Pfizer, Regeneron, and EMD Serono; has served on the advisory board for Bristol-Myers Squibb; holds equity in Biond, Evaxion, OncoC4, and Instil Bio; and is on scientific advisory board for CytomX, Incyte, ImCheck, Biond, Sellas, Instil Bio, OncoC4, and Neximmune. His institution has received research support from Bristol-Myers Squibb, Merck, GSK, Moderna, Pfizer, Novartis, and AstraZeneca.

Suggested Readings

Khattak A, Weber JS, Meniawy T, et al. Distant metastasis-free survival results from the randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial [ASCO abstract LBA9503]. *J Clin Oncol*. 2023;41(17)(suppl).

Palmer CD, Rappaport AR, Davis MJ, et al. Individualized, heterologous chimpanzee adenovirus and self-amplifying mRNA neoantigen vaccine for advanced metastatic solid tumors: phase 1 trial interim results. *Nat Med*. 2022;28(8):1619-1629.