Pembrolizumab approval is tip of the iceberg for immunotherapy in head and neck squamous cell carcinoma

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The recent approval of pembrolizumab (Keytruda) in recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) following progression on a platinum-based chemotherapy was a significant advancement for the disease. However, the approval of the PD-1 inhibitor only scratches the surface of the potential of immunotherapies in head and neck cancer, said Barbara A. Burtness, MD.

"Immunotherapy is a big change for head and neck cancer and there seems to be no doubt that there is activity for immunotherapies with pembrolizumab as well as nivolumab [Opdivo]" said Burtness, professor of Medicine, clinical research program leader, Head and Neck Cancers Program at Yale Cancer Center.

"But one question that still remains is, 'Will there be a role for these agents in first-line therapy for patients with metastatic recurrent disease who have not previously failed a platinum-based approach?'" added Burtness.

In an interview with OncLive, Burtness discussed the potential role for immunotherapy in frontline head and neck cancer, as well as the possible benefit of using it in combination with standard treatments, including radiation and chemotherapy.OncLive: What ongoing immunotherapy research in head and neck cancer are you particularly excited about?Burtness: There are 3 trials that are currently ongoing to look at

the use of immunotherapy in first-line treatment of metastatic recurrent head and neck cancer. Two of the trials are looking at combinations of a CTLA-4 drug with a PD-1 agent compared with standard chemotherapy with cetuximab (Erbutix). There is another trial in which the question asked is, "How do we combine chemotherapy with immunotherapy?" This is a trial with pembrolizumab monotherapy versus pembrolizumab with chemotherapy, versus chemotherapy with cetuximab, which serves as the FDA standard.

The reason I am very excited about that trial is because one of the things that have plagued us a bit with immunotherapies in head and neck cancer is that the response rates are a little bit modest. With the pembrolizumab data that led to the FDA approval, the response rate was about 18%. For patients who are symptomatic, have bulky disease in the neck, and are at risk with the airway or at risk for bleeding, an 18% response rate isn't really that high.

The [idea] of whether or not adding chemotherapy will lead to a rapid response, and then integrating it with immunotherapy to a much more durable response is pretty intriguing. The trial is accruing well and that is an answer that we should have within a year or so.Why might the combination of pembrolizumab and chemotherapy be synergistic?Right now, we don't know if it would necessarily even need to be synergistic to be beneficial. Could a patient get an independent benefit from immunotherapy and from chemotherapy at the same time? That is the simplest explanation as to why it may be better. You would have the reliability of the chemotherapy response, and you would add to that the durability of the immunotherapy response.

The other thing that is very appealing about immunotherapy is, obviously, its tolerability. Whether chemotherapy integrated with immunotherapy will be highly tolerable is something we will learn from the trial. Is there a way that you could imagine that there would be

synergy? Yes, absolutely. The leading hypothesis in my mind is that the chemotherapy that we use in head and neck cancer causes DNA damage and cell death and, as the cells die, they release antigens. As you have DNA damage, you create mutations that may lead to novel antigens. The possibility that there really could be a uniquely synergistic effect, where each drug amplifies the benefit of the other, is very intriguing. We need to see if that is what happens.Besides chemotherapy, are there other ways immunotherapy is being used with standard therapy in head and neck cancer?One of the other ways to integrate standard therapy with immunotherapy is with the addition of radiation therapy. There are 3 ways to do that: give the immunotherapy first, give it during radiation, or administer it after the radiation.

It is pretty clear that the administration of radiation changes the tumor-immune microenvironment, so there are lots more tumor-infiltrating lymphocytes (TILs) and transient upregulation of PD-1 expression.

We have a trial that is currently ongoing here at Yale Cancer Center where patients with persistent disease after chemoradiation that is biopsy proven receive immunotherapy with pembrolizumab. The hypothesis is that the upregulation of PD-1 and the augmentation of the TILs will create a better environment for the use of the immunotherapy. We are hoping to learn whether or not the response rate is higher in that post-radiation setting.

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