



Barbara Burtness, MD

A Big Advance in Treatment of Head and Neck Cancers

The standard treatment for patients whose head and neck cancer has either recurred or metastasized had not improved since 2006. “It’s a three-drug cocktail,” said Barbara Burtness, MD, Professor of Medicine and Co-Director of the Developmental Therapeutics Research Program. “It’s a hard treatment. The response rate is just 35 or 40 percent and the average survival is under 11 months. So we’ve been looking for something that would work better, to allow patients to live longer and avoid the toxicity of this regimen.”

That something might be an immunotherapy drug called pembrolizumab. An earlier trial showed that pembrolizumab was more effective for patients with head and neck cancer who had failed first line chemotherapy than selecting a second chemotherapy. Dr. Burtness wanted to test whether pembrolizumab alone, as a first-line drug, increased survival for patients with biomarkers that predicted a response to pembrolizumab, and whether using it in combination with chemotherapy would be more effective even without the biomarker selection.

Pembrolizumab is an immune checkpoint inhibitor. It blocks the receptor activated by a protein called PD-L1, which allows cancer cells to escape detection by the immune system. When pembrolizumab seeks out the receptor, PD1, the immune system wakes up and starts attacking cancer cells. But many tumors don’t express this biomarker, and some express it at low levels.

“We had two hypotheses,” explained Dr. Burtness of her trial, named Keynote-048. “One was that if you

had enough of the biomarker PD-L1, you were a good candidate for immunotherapy, and that maybe getting immunotherapy alone would be sufficient. The other hypothesis was that combining pembrolizumab with chemotherapy might be beneficial because chemotherapy does lead to response in and of itself, and maybe the cell death caused by chemotherapy would not only help control the disease, but potentially could release proteins that would be targets for the immune system, and thus make patients who weren’t that sensitive to immunotherapy more sensitive to it.”

Keynote-048 was a large trial involving almost 900 patients. All were tested for their level of PD-L1 expression and then randomly divided into three groups. One group received only pembrolizumab. A second group got pembrolizumab plus platinum-based chemotherapy. The third group was treated with the standard three-drug cocktail.

In October, Dr. Burtness presented interim findings of this phase 3 trial at the annual meeting of the European Society for Medical Oncology (ESMO). For patients with the PD-L1 biomarker, pembrolizumab alone was much more effective than the current standard of care. Patients who took a combination of pembrolizumab and chemotherapy also did better than patients using the standard treatment, even without using a biomarker to select patients.

“The median overall survival is longer, the one-year overall survival is higher, and the two-year overall survival is higher,” said Dr. Burtness. In short, patients who receive

pembrolizumab live longer than those who don’t.

To people outside of cancer research, an improvement in median survival of four months might seem small, but Dr. Burtness calls it substantial. She points out that 14.9 months represents median survival, which means that 50 percent of the patients lived longer than that, sometimes much longer, as demonstrated by the fact that some people had responses that lasted over 21 months.

“And there were some patients who had complete responses,” she added. “They were able to stop treatment and have had no recurrence of their disease. That’s an exceedingly rare event with the older chemotherapy regimen. Giving pembrolizumab early has the ability to change the natural history of head and neck cancer. That fills us all with hope that moving this treatment into the curative setting will have a profound effect.”

Dr. Burtness’ results offer strong evidence that pembrolizumab alone or with chemotherapy is superior to the current standard of care for head and neck cancers. She hopes her findings lead to FDA approval of the drug as a first-line treatment. Meanwhile, she and her colleagues are studying how best to use pembrolizumab in patients with earlier stages of the disease who are being treated with chemotherapy and radiation. She is also exploring the drug’s use in patients with radiotherapy resistance. “We’ve seen complete responses in that setting,” she said.

It seems clear that patients with head and neck cancers soon won’t have to settle for the unpleasant three-drug cocktail.