In June, for the first time in a decade, the FDA approved a new first-line treatment for patients with metastatic or recurrent head and neck cancer (HNC). These cancers are notoriously difficult and painful to treat, typically with poor outcomes, so a new approach was overdue. This treatment uses the immunotherapy drug pembrolizumab (Keytruda) for patients with metastatic or recurrent HNC, either alone or in combination with chemotherapy. The new regimen improves on the old standard of care (three chemotherapy drugs) by dramatically improving survival rates, both short-term and long-term. When it is given alone, it is also significantly less toxic.

These life-changing advances, as well as the FDA’s approval, stem from research done by physician-scientists at Yale, particularly through the leadership of Barbara A. Burtness, MD, Professor of Medicine and Co-Leader of the Developmental Therapeutics Research Program. Dr. Burtness directed a large, international, randomized phase III clinical trial whose results persuaded the FDA to approve the new treatment.

Pembrolizumab is an immune checkpoint inhibitor that blocks the expression of PD-L1, a protein that camouflages cancer cells and allows them to elude the immune system. By blocking PD-L1, pembrolizumab strips away cancer’s camouflage. The immune system then detects the invaders and attacks. Not all tumors express this biomarker, and some express it at low levels.

The trial, directed by Dr. Burtness, involved almost 900 patients divided into three groups: one received pembrolizumab alone, another was treated with pembrolizumab plus chemotherapy, and a third was given the older standard treatment of chemotherapy plus an antibody called cetuximab. The patients had varying levels of PD-L1.

Dr. Burtness presented the interim findings in Munich last October at the annual meeting of the European Society for Medical Oncology (ESMO). The data were clear: Patients who received pembrolizumab did better than those who did not.

Since then, Dr. Burtness and her colleagues have been digging deeper into the data. In June, updated findings were presented at the annual meeting of the American Society of Clinical Oncology (ASCO). The researchers looked specifically at the two groups of patients who received chemotherapy—one with pembrolizumab and the other with the standard of care. They broke down the results according to the patients’ expression of PD-L1. Among those with higher levels of PD-L1, the addition of pembrolizumab to chemotherapy made a large difference in median survival—14.7 months compared to 11 months for patients on the standard regimen.

“That was very statistically significant,” said Dr. Burtness. “The other remarkable thing was the durability of the effect.” After two years, 35 percent of the people who had received...
pembrolizumab were still alive, compared to 19 percent of those who received conventional chemotherapy. After three years these survival rates were 33 percent and eight percent, respectively.

“So between 24 months and 36 months,” explained Dr. Burtness, “there continued to be a significant falloff in the conventional group but the survival rate had stabilized in the pembrolizumab group. That durable effect is very significant.”

Next the researchers looked more closely at patients whose tumors expressed smaller amounts of PD-L1. Again, they found a strong effect. The median survival with conventional chemotherapy was 10.4 months, but adding pembrolizumab raised that number to 13.6 months. The scientists also found similar patterns of stability and durability. The survival rate for those on conventional chemotherapy plummeted over time, whereas patients who were treated with pembrolizumab lived longer and the survival rate stabilized: after three years, 25.6 percent of the pembrolizumab patients were alive compared to 6.5 percent of those who had conventional therapy.

“Then we looked to see if there were subgroups that didn’t seem to benefit from pembrolizumab,” said Dr. Burtness. “But every single subgroup we looked at—whether based on age, gender, or performance status or region of the world...or whether they had recurrent disease only or also had metastatic disease—across all those groups, pembrolizumab was better than conventional treatment.”

Dr. Burtness and her colleagues found that both conventional chemotherapy and pembrolizumab with chemotherapy initially showed similar success at stopping the cancer’s progression. “But as time went by,” she said, “the patients who were not progressive early on pembrolizumab plus chemotherapy were more likely to have durable effects. I think our trial shows that you should expose patients to pembrolizumab early because we have these durable survival effects even after patients progress and come off pembrolizumab. It appears as if reinvigorating the immune system early in the course of treatment makes a big difference. We hypothesize that pembrolizumab may sensitize tumors to subsequent therapies.”

The researchers also updated their data comparing conventional chemotherapy to pembrolizumab as a monotherapy. The median survival was 10.7 months for patients on conventional treatment versus 14.8 months for pembrolizumab alone. “And, again, I’m going to harp on durability,” said Dr. Burtness, “because at three years 29 percent of the patients who got pembrolizumab were alive as opposed to nine percent who got the standard of care therapy. So as the data have matured,” she concluded, “they only get more impressive. We saw the effects holding across all groups.” That’s what the FDA saw as well. It decided that HNC patients with higher expression of PD-L1 can be treated with pembrolizumab alone as a first-line monotherapy, and that all patients, regardless of their levels of PD-L1, can receive the drug in combination with chemotherapy as a first-line treatment.

Meanwhile, Dr. Burtness is immersed in additional clinical trials concerning HNC. One involves patients who are radiotherapy-resistant. The standard of care for these patients is major surgery, often with terrible after effects, and their cancer typically recurs quickly. In the trial at Yale, patients receive four doses of pembrolizumab before surgery. “The hope is that the immunotherapy will reverse the exhaustion of the patient’s immune system and allow it to recognize the cancer again so that the operation can be more successful,” explained Dr. Burtness. She added that it’s too early to discuss results, but notes that some responses have been remarkable.

Another trial beginning this fall will treat HNC with a combination of immunotherapy and an HPV vaccine. Her lab is also exploring targeted therapies, which haven’t been individually successful against HNC. But in a paper published in February in Clinical Cancer Research, she and colleagues found that simultaneously targeting and inhibiting two oncogenic kinases, Aurora Kinase A (AURKA) and WEE1, creates a spectacular synergistic response in the HNC squamous cell carcinoma.

“The cells kind of explode,” said Dr. Burtness. “It looks like a nova.” The researchers have demonstrated this destructive synergy in HNC cell lines and mouse models, and hope to move into a clinical trial shortly. “It’s pretty exciting,” said Dr. Burtness.