pembrolizumab were still alive, compared to 39 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 fallout 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 33.6 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 treatment.

"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, whether they had been smokers, or their disease was related to HPV [human papillomavirus], 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 even after patients progressed and came to have durable effects. I think our trial shows that you should early on pembrolizumab plus chemotherapy were more likely as time went by," she said, "the patients who were not progressive showed similar success at stopping the cancer's progression. "But every single subgroup we looked at—whether based on age, gender, or performance status or region of the world, whether they had been smokers, or their disease was related to HPV [human papillomavirus], or whether they had recurrent disease only or also had metastatic disease—across all those groups, pembrolizumab was better than conventional treatment."

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.

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Mr. Metz's chronicle began in 2003 when his dermatologist biopsied a mole on his back and discovered stage II melanoma. Mr. Metz was referred to surgeon, Stephan Artyian, MD, MBA, where he underwent wide excision surgery, which removes the tumor and a margin of assumed healthy tissue around it. In addition, nearby lymph nodes were checked and a biopsy was taken of the sentinel lymph node, the lymph node that drains the tumor. For Mr. Metz, all lymph nodes were found to be clear and he finally felt that he could exhale. He was then referred to Harriet Kluger, MD, Professor of Medicine (Medical Oncology), to be monitored.

“I felt like I had dodged the bullet,” recalled Mr. Metz. “The doctors had me check in with them each year to make sure nothing had spread to other organs in my body. All was fine until a few years later when I started waking up in the middle of the night due to night sweats.”

Mr. Metz's primary doctor sent him for an ultrasound, which revealed an 11-centimeter tumor on his liver, later determined to be a metastasis from the melanoma on his back. “I was shocked and surprised that the melanoma cells had escaped into the bloodstream and gone from my back to my liver years later,” Mr. Metz said.

“Dr. Kluger explained that if we did not do anything, I only had a matter of months to live. This news sent me into a tailspin. I came out of it in a way that I call my fight mode. I wanted to become an expert in my disease. I immediately went on the internet to find out any information I could. I wanted to really understand my options and what possible treatments could beat this disease.”

The choices of treatment for stage IV melanoma in 2008 were very limited, either chemotherapy—which had limited success, or a form of immunotherapy, high-dose interleukin-2, which required two five-day hospital stays, with one week off in between, followed by scans to see the results of the treatment. Mr. Metz chose to proceed with the interleukin-2, but after completing the treatment, his scans did not show any changes in the tumor.

Dr. Kluger recommended that Mr. Metz visit the National Cancer Institute (NCI) in Bethesda, Maryland for an investigational treatment where he would be considered for a clinical trial for tumor infiltrating lymphocyte therapy (TIL), which activates immune cells to recognize and attack cancer cells. This modality was not available at the time at Yale, but it is now.

Unfortunately, Mr. Metz's blood test revealed high liver enzyme levels from the tumor in his liver, which indicated he was not a candidate for the TIL investigational trial. Instead, the doctors at the NCI recommended surgery to remove as much of the tumor on his liver as possible. They also explained that there was a small chance (15-20 percent) he would not survive the surgery. Considering his chances of survival without surgery were 2-3 months, it was an option he and his family considered. They also explained that there was a small chance NCI recommended surgery to remove as much of the tumor on his liver, which indicated he was not a candidate for the TIL investigational trial. Instead, the doctors at the NCI recommended surgery to remove as much of the tumor on his liver as possible. They also explained that there was a small chance (15-20 percent) he would not survive the surgery. Considering his chances of survival without surgery were 2-3 months, it was an option he and his family considered. They also explained that there was a small chance (15-20 percent) he would not survive the surgery. Considering his chances of survival without surgery were 2-3 months, it was an option he and his family considered. They also explained that there was a small chance (15-20 percent) he would not survive the surgery. Considering his chances of survival without surgery were 2-3 months, it was an option he and his family considered. They also explained that there was a small chance (15-20 percent) he would not survive the surgery. Considering his chances of survival without surgery were 2-3 months, it was an option he and his family considered.

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Following the surgery, Mr. Metz continued to return to Bethesda periodically for the next three years for scans and checkups. “All was well,” said Mr. Metz, “until a scan showed that the melanoma had metastasized to my brain. I was devastated because I had been thinking that if something happened, the TIL treatment would be my savior. And now brain mets (metastases) would preclude me from getting that treatment.”

Mr. Metz called Dr. Kluger, who explained the available options and introduced him to Veronica Chiang, MD, FAANS, Professor of Neurosurgery, in March 2011. After further consultation, Dr. Chiang recommended he be scheduled for a Gamma Knife procedure. The Gamma Knife treatment allows a team of radiation therapists and neurosurgeons to give high doses of radiation to a very targeted area of the brain. “After the treatment, my life pretty much went back to normal again.”

It was at this time that Mr. Metz wanted to make a difference. He launched The Brain Metastasis Fund to raise money and support Yale Cancer Center’s research efforts. “My doctors had been great to me and I wanted to give back. I relied on my former experience working in the insurance and financial industries to begin this initiative. I invited 100 people to a party in my backyard. Seventy-five showed up and we started raising money. To date, we have raised over $700,000 from private donations,” said Mr. Metz.

In fact, one of the major research initiatives resulting from The Brain Metastasis Fund was to support Yale Cancer Center initiated clinical trials that provide access to promising drugs prior to their approval by the FDA. One such class of immunotherapy was showing highly promising results at the time, but patients with brain metastases were traditionally excluded from those trials. Therefore, the team at Yale used the funding to initiate the first study of pembrolizumab for patients with brain metastases from melanoma or lung cancer. In 2014, Mr. Metz was accepted into the clinical trial.

After starting on pembrolizumab, which at the time was a much higher dose of the drug than was used today, no brain metastases developed. However, Mr. Metz could not tolerate the higher dosage and he was taken off the trial and instead placed on the FDA-approved dosage of pembrolizumab, which allowed stabilization of the disease and for Mr. Metz to recover functionally to where he is today.

“I have the highest regard for Dr. Kluger. She is incredibly smart and talented. And she’s never given up on me. She continues to find new ways to keep me going. Today, I’m still on pembrolizumab along with phenobarbital to lessen the side effects. If it wasn’t for her and her team, I would not be alive today.”

Mr. Metz cherishes the encouragement and assistance that his wife of 46 years, his two sons, and his grandchildren have given him. “They continue to be my greatest joy. I treasure the time I spend with my family. My cancer has changed my perspective and my life. I have looked at myself and set new priorities. I am fortunate to be surrounded by good doctors, a wonderful family, and many friends. I know that there is a tremendous amount of work being done in the research field. That gives me hope that someday I will be totally healed.”

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