

Two new clinical trials, led by Yale investigators, aim to increase survival for women with triple-negative breast cancer (TNBC). That result is long overdue—the last significant improvement in outcome against early-stage disease appeared more than 20 years ago.

Both trials will explore the effectiveness of immunotherapies against early-stage TNBC, says their designer and principal investigator, Lajos Pusztai, MD, DPhil, Professor of Medicine, Chief of Breast Medical Oncology, and Co-Director of the Cancer Center's Genomics, Genetics, and Epigenetics Program. Immunotherapy drugs, particularly immune checkpoint inhibitors, rev up the immune system against cancer cells.

"These drugs work remarkably well in lung cancer, melanoma, head and neck cancers, and bladder cancer, but breast cancer is a latecomer to this field," Dr. Pusztai explains. "About 7 years ago we and others noted that breast cancers with high levels of immune infiltration have excellent survival. However, at that time there were no drugs to test if this association represented a cause and effect relationship or a mere coincidence. This has changed with the development of immune checkpoint inhibitors."

Most current immunotherapy trials for breast cancer are focused on advanced, metastatic disease, not early-stage cancer, as the two groundbreaking trials do at Yale. "We need more effective treatments in early-stage disease, where the impact is greater," says Dr. Pusztai. "It's important to prolong a patient with metastatic breast

cancer's life for several months, or even years; but it is even more important to cure a person when her cancer is first diagnosed and prevent metastatic recurrence, as we can do in early-stage breast cancers."

Right now the best weapon against early-stage TNBC is chemotherapy that is often administered before surgery. After treatment, about a third of the patients show no traces of cancer at the time of surgery, which oncologists call a pathologic complete response. Unfortunately, the majority of patients don't achieve this.

One way to improve these outcomes is to increase the effectiveness of preoperative chemotherapy. One of the trials (NCT02489448) led by Dr. Pusztai aims to accomplish exactly this by adding durvalumab (MEDI4736), anti-PD-L1 immune checkpoint therapy, to the best currently available chemotherapy regimen. In December 2015, the first patient to receive the combination of standard chemotherapy plus anti-PD-L1 therapy as preoperative treatment for TNBC was on the clinical trial at Yale. The phase I part of the study is completed. The results haven't been published, but Dr. Pusztai says, "Our patients did well without major toxicities and there were many pathologic complete responses." The phase II part of the study will begin at Smilow Cancer Hospital early in 2017.

The second clinical trial (NCT02954874) is for TNBC patients who have extensive cancer after completion of standard preoperative chemotherapy. This is a national, randomized trial to test if one year of treatment with the

anti-PD-1 antibody pembrolizumab could improve survival in these patients. "If chemotherapy didn't work," says Dr. Pusztai, "maybe stimulating the immune system will, and perhaps it can eradicate the micro-metastatic cancers that survived the preoperative chemotherapy."

Pembrolizumab, an anti-PD-1 antibody, has already been approved against several advanced cancers, and has also been tested against metastatic TNBC in one phase I trial, done at Yale and elsewhere. In that study, the tumors shrank in about 20 percent of the patients, comparable to, or even better than chemotherapy could do in a similar situation. Remarkably, many of the patients who responded to the treatment remained on therapy for close to a year, indicating prolonged disease control, which is rarely seen with chemotherapy in this clinical setting.

Dr. Pusztai is testing immunotherapy drugs against TNBC partly because it often contains more tumor-infiltrating lymphocytes (TILs) than other subtypes of breast cancer. That could be good news in terms of immunotherapy, since more TILs mean more T-cells that can be activated to attack the cancer. In a small fraction of TNBC, TILs account for 50 percent or more of the cells in the micro-environment of the cancer and the prognosis for such patients, after chemotherapy and surgery, is excellent. But, the majority of TNBC contains much fewer TILs. The idea behind these trials, says Dr. Pusztai, is to force tumors with a low percentage of lymphocytes to act like tumors with 50 percent or more.

Lajos Pusztai, MD, DPhil

Boosting the Immune System to Fight Breast Cancer