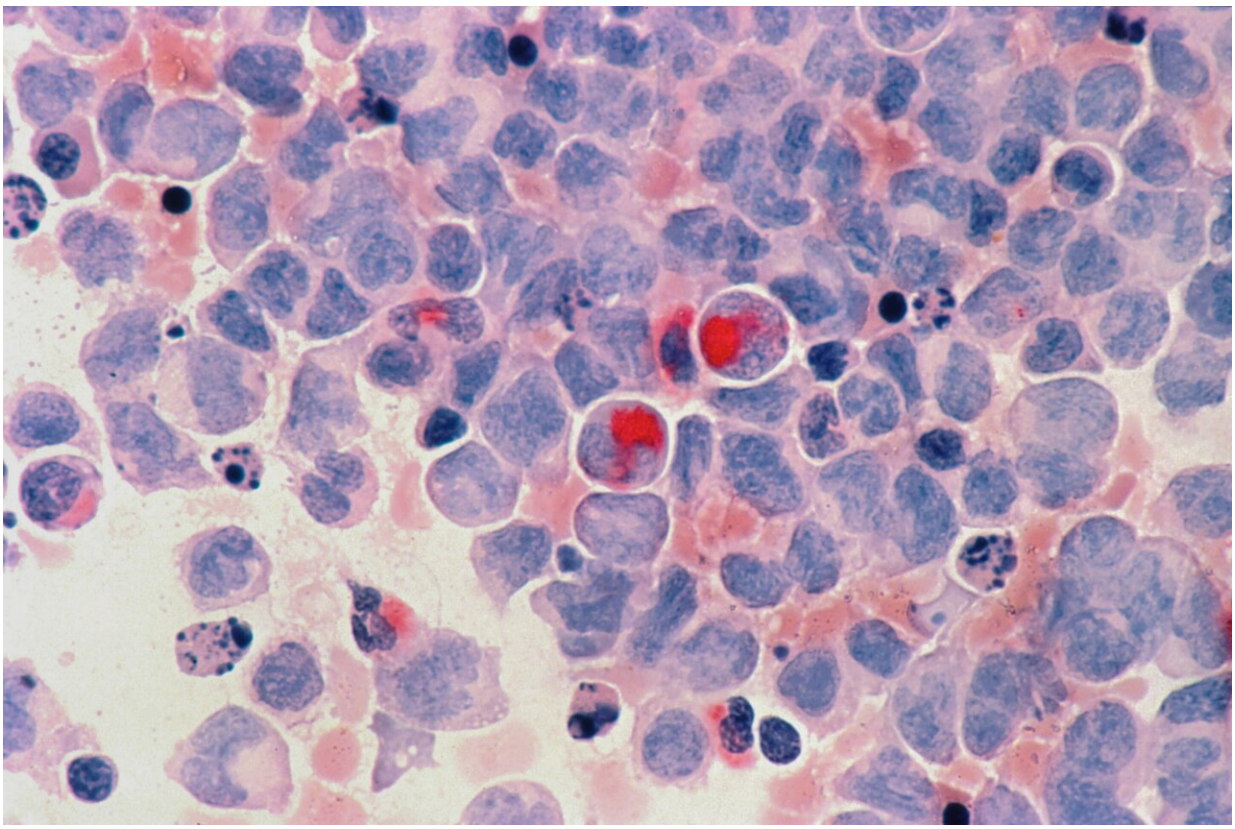
Investigators profile three treatment response trajectories to close in on triple-negative breast cancer

January 8 2024



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Cedars-Sinai Cancer investigators have analyzed the cells within triple-negative breast cancer tumors before and after radiation therapy with

immunotherapy, identifying three patient groups with different responses to the treatment. Their study, published in *Cancer Cell*, found that for some patients with this difficult-to-treat cancer, radiation therapy plus immunotherapy could yield the best tumor-fighting immune response prior to surgery.

"Our most important finding was identifying these three different patient groups," said Simon Knott, Ph.D., co-director of the Applied Genomics Shared Resource at Cedars-Sinai Cancer and senior author of the study.

One group, Knott said, didn't respond at all to therapy, one responded well to immunotherapy, and one responded only to immunotherapy plus radiation therapy. "This could help us employ our most aggressive treatment options only when needed most," Knott said.

Triple-negative breast cancer is so called because its cells test negative for receptors to the hormones estrogen and progesterone and for a protein called HER2. These tumors, which account for 10%-15% of breast cancers, grow and spread faster than other types and, in general, have fewer treatment options.

Patients with triple-negative breast cancer generally receive treatment to shrink their tumors before having surgery. Immunotherapy, which uses a person's own immune system to fight cancer, is part of that pre-surgical treatment.

"Triple-negative breast cancer is the only type of breast cancer we treat with immunotherapy," said Stephen Shiao, MD, Ph.D., co-director of the Cancer Therapeutics Program at Cedars-Sinai Cancer and first author of the study. "Unfortunately, only 20% to 30% of patients respond to immunotherapy on its own. Combining it with chemotherapy boosts response to 60% but exposes patients to significant toxicity."

To determine whether a combination of radiation therapy and immunotherapy would improve patient response, investigators launched a clinical trial. During the trial, they examined tumors from 34 triple-negative breast cancer patients.

Patients underwent biopsies before treatment, after one course of immunotherapy, and after a second course of immunotherapy plus radiation therapy. Investigators then analyzed the biopsied tissues.

They used single-cell genetic profiling to identify the cancer cells and different types of immune cells making up each tumor. They also looked at proteins expressed by cells, mapping their positions and permitting a better understanding of how the different cells interact.

The analysis yielded profiles for three types of responders, Knott said.

"We saw that tumors of patients who didn't respond at all to pre-surgical therapy had no immune cells in them, and tumors of patients who responded right away to immunotherapy were packed with certain types of immune cells," Knott said. "That wasn't surprising. But we found another group of patients with tumors that looked quite similar to the tumors of non-responders and didn't respond to the initial round of immunotherapy.

"However, they did respond after the combination of immunotherapy and radiotherapy. After the combination therapy, immune cells invaded the tumors, and the tumors shrank."

Dan Theodorescu, MD, Ph.D., director of Cedars-Sinai Cancer and the PHASE ONE Distinguished Chair, said that the study's findings suggest radiotherapy may positively impact immune response in these tumors.

"This study will guide investigators toward the next generation of clinical

trials," Theodorescu said. "The investigators also describe a new framework for mapping the distribution of immune cells within tumors, and that could help us identify new precision medicine approaches for patients with breast and other cancers."

Investigators' next task is to find practical ways to identify these responder groups in a clinical setting via blood samples or other means to better tailor treatments. They will also explore the possibility of combining radiotherapy with other types of immunotherapy prior to surgery as a way to improve patient response for high-risk patients, Shiao said.

More information: Theodorescu et al, Single-cell and spatial profiling identify three response trajectories to pembrolizumab and radiation therapy in triple negative breast cancer, *Cancer Cell* (2024). DOI: 10.1016/j.ccell.2023.12.012. www.cell.com/cancer-cell/fullt … 1535-6108(23)00440-3

Provided by Cedars-Sinai Medical Center

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