

Breast cancer is the most common type of cancer diagnosed in women, which will affect 1 in 8 women in their lifetime. There are several different subtypes of breast cancer, each of which has unique biological features and treatment options. Hormone receptor-positive (HR+) breast cancer is the most common subtype, which accounts for roughly 70% of cases. The growth of HR+ breast tumors is fueled by the hormone estrogen, which binds to the estrogen receptor on the surface of tumor cells. Thus, HR+ breast cancer is treated with endocrine therapy, a type of targeted therapy that blocks the estrogen receptor or depletes estrogen within the body.

When diagnosed in the early stages (stages I-III), HR+ breast cancer can be successfully treated with surgery, radiation therapy, and endocrine therapy. Unfortunately, this type of cancer can recur years later, either in the breast or elsewhere in the body. Once it has spread throughout the body, the cancer is considered metastatic (stage IV), at which point it is incurable.

Patients with HR+ metastatic breast cancer (MBC) are initially treated with endocrine therapy, often in combination with another targeted agent like an inhibitor of CDK4/6 or PI3K. These treatment combinations can prevent the cancer from spreading for several years. Unfortunately, HR+ MBC inevitably develops resistance to the initial treatment regimen and begins progressing through all available combinations of endocrine therapy plus other targeted agents despite treatment. At this point, patients are treated with a series of chemotherapeutic agents, each of which only prevents the cancer from spreading for several months, often with substantial side effects. Newer targeted therapies with greater efficacy and fewer side effects are urgently needed for patients with HR+ MBC.

Immune checkpoint inhibitors (ICIs) are antibodies that enhance the cancer killing ability of immune cells. ICIs have shown promise in many types of cancer, including melanoma, lung cancer, and triple-negative breast cancer. Unfortunately, ICIs have been less successful in treating HR+ MBC. This treatment resistance is likely due to the tendency of HR+ MBC tumors to exclude cancer-killing immune cells and suppress their activity inside the tumor. To enhance the effectiveness of ICIs in HR+ MBC, it is crucial to identify the mechanisms by which the tumors keep immune cells out and suppress their activity.

The present study aims to answer this unmet clinical need by evaluating a new therapeutic combination consisting of sacituzumab govitecan and the ICI pembrolizumab in patients with HR+ MBC. Sacituzumab govitecan is an antibody-drug conjugate, meaning it consists of a cell-killing molecule called SN-38 attached to an antibody that recognizes cancer cells. When the antibody binds to cancer cells, SN-38 is released inside and outside the cancer cells, resulting in cell death. Sacituzumab govitecan targets cancer cells more selectively than standard chemotherapy, which kills cancer cells and healthy dividing cells indiscriminately. In a recently completed clinical trial of patients with endocrine-resistant HR+ MBC, sacituzumab govitecan halted disease progression for a median of 5.5 months, which is longer than typically seen with chemotherapy.

Importantly, experiments in mice suggest that sacituzumab govitecan may enhance the immune response against tumors and work in concert with ICIs like pembrolizumab, an inhibitor of PD-1. PD-1 is a protein expressed on immune cells that restricts their killing ability. Many cancer cells express proteins that bind to PD-1, which protects them from being killed by the immune cells. ICIs like pembrolizumab block PD-1, which prevents cancer cells from binding and unleashes the cancer-killing ability of immune cells. We hypothesize that the combination of these two therapies will produce longer responses than sacituzumab govitecan alone by better activating immune cells to kill cancer cells.

Our research will test this hypothesis by investigating the effect of this novel therapeutic combination on immune cell recruitment and activation in MBC tumors. Comprehensive molecular and genomic studies on paired tumor samples collected before and during treatment will evaluate changes in immune cells with treatment at a single cell level. Altogether, this work will broaden our understanding of the biological mechanisms underlying resistance to this novel combination therapy. Most importantly, these findings have the potential to reveal new immunotherapeutic targets that can be exploited to accelerate the development of more effective treatments for patients currently living with HR+ MBC.