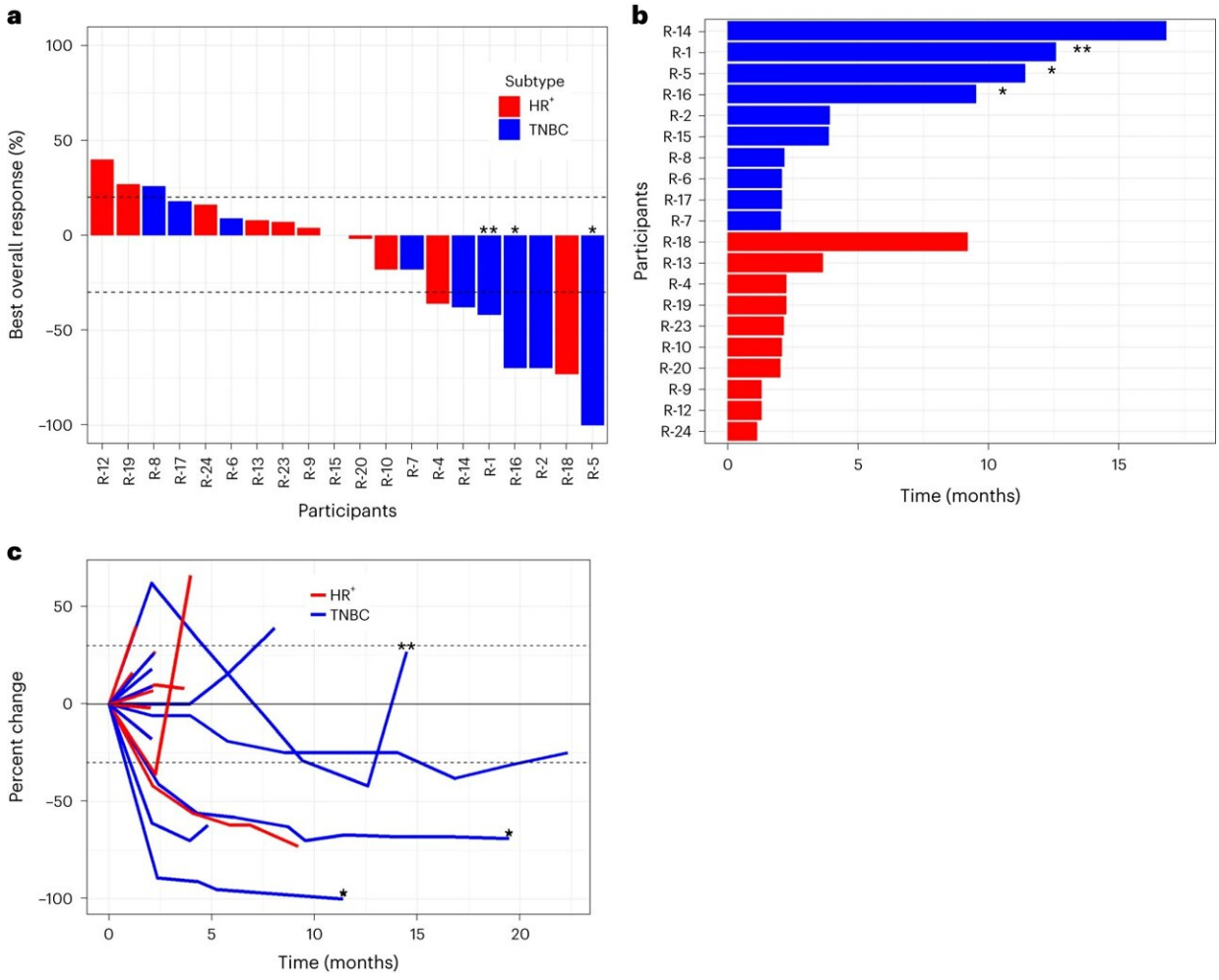
Novel drug combination shows promise for advanced HER2-negative breast cancer

February 14 2024



Clinical efficacy. **a**–**c**, Responses as shown by a waterfall plot (**a**), swimmers plot (**b**) and spider plot (**c**). The dashed lines correspond to +20% and –30%, respectively. The single asterisk (*) identifies participants with continued benefit beyond data cutoff. Double asterisks (**) identify participants with response after treatment beyond progression; $N = 20$ participants. Credit: *Nature Cancer*

(2024). DOI: 10.1038/s43018-024-00729-w

A novel three-drug combination achieved notable responses in patients with advanced HER2-negative breast cancer, according to new research directed by investigators from the Johns Hopkins Kimmel Cancer Center.

The treatment included a histone deacetylase (HDAC) inhibitor—a drug that causes a chemical change to stop tumor cells from dividing—with two types of immunotherapy known as checkpoint inhibitors, which unharness the power of the immune response against cancer.

The multicenter phase IB study, which aimed to improve response to checkpoint inhibitors by sensitizing the tumor microenvironment, found that the combination therapy resulted in a 25% overall response rate (ORR) in women with advanced HER2 (human epidermal growth factor receptor 2)-negative breast cancer.

This means that for 25% of women who received the therapy, their cancer was destroyed or significantly reduced. Patients with triple-negative breast cancer, who have fewer treatment options than patients with other breast cancers, had an ORR of 40%. These results were published in *Nature Cancer*.

"Our findings show that pre-treatment with the HDAC inhibitor entinostat and the use of dual immune checkpoint inhibitors is a safe and promising strategy for metastatic breast cancer, warranting further clinical evaluation in a phase II study," says lead author Evanthia Roussos Torres, M.D., Ph.D., an assistant professor at the University of Southern California Keck School of Medicine who was at the Johns Hopkins University School of Medicine and Kimmel Cancer Center

when the work was conducted.

"These results certainly met our hypothesis that we could improve response to checkpoint inhibition in metastatic breast cancer."

This study was conducted across four clinical sites and included 24 women with HER2-negative metastatic breast cancer. Twelve had hormone receptor-positive disease, and 12 had the triple-negative disease. All received entinostat plus two types of immunotherapy: the PD-1/PD-L1 inhibitor nivolumab and the CTLA-4 inhibitor ipilimumab.

The study met its primary endpoint of safety by demonstrating that there were expected and tolerable toxicities among patients, with none requiring discontinuation of therapy. The average progression-free survival (PFS) was 50% at six months, meaning for half of the participants, their disease did not worsen for at least six months. Future studies will address the treatment's efficacy.

"To our knowledge, this is the first published study that investigates treatment with an HDAC inhibitor in combination with dual immune checkpoint inhibitor therapy in patients with advanced breast cancer," says co-author Elizabeth Jaffee, M.D., the Dana and Albert "Cubby" Broccoli Professor of Oncology and deputy director of the Johns Hopkins Kimmel Cancer Center.

"Heavily pre-treated advanced breast cancer remains an area of unmet need, and a combination strategy that results in the ORR and PFS described is of interest."

For many patients with solid tumors, immune checkpoint inhibitors have become cornerstones of treatment by releasing the inhibition function of various types of immune cells and allowing patients' immune systems to attack cancer cells. This strategy has so far been ineffective for most

breast cancers.

Conversely, epigenetic drugs that silence the genes involved in cancer development have been studied with single immune checkpoint inhibitors for breast cancer to change the immune response in the tumor microenvironment. Dual immune checkpoint inhibitors have been shown to be safe when used in combination for a variety of cancers.

"Although we did see very good responses, the question is whether we did it by changing the tumor microenvironment, but the study was not powered to answer this question," Roussos Torres says. "Our study highlights the need for a deeper investigation of the breast cancer tumor microenvironment with a focus on changes in myeloid (immune) cell populations to determine their role in sensitization of the tumor microenvironment to treatment with immune checkpoint inhibitors."

"This clinical trial highlights the importance of interdisciplinary collaboration to bring an exciting hypothesis from the laboratory to the clinic, and sets the scene for future trials investigating novel treatment approaches for this patient population," says Roisin Connolly, M.D., M.B.B.Ch., who was lead principal investigator for the trial alongside Vered Stearns, M.D. Connolly is now at the University College Cork in Ireland. Stearns is now at Weill Cornell Medicine in New York.

About 300,000 people in the United States receive a breast cancer diagnosis each year, making it the most common cancer among American women apart from skin cancers. Of these, about 70% are hormone receptor-positive and HER2-negative, meaning the tumor cells contain receptors for estrogen or progesterone but low levels of the protein HER2.

Only about 10% to 15% of breast cancer cases are what's known as triple negative, meaning tumor cells have no hormone receptors and low HER2

levels, making them more difficult to treat than other types of breast cancer.

More information: Evanthia.T. Roussos Torres et al, Entinostat, nivolumab and ipilimumab for women with advanced HER2-negative breast cancer: a phase Ib trial, *Nature Cancer* (2024). DOI: 10.1038/s43018-024-00729-w

Provided by Johns Hopkins University School of Medicine