Background Breast cancer remains a significant global health challenge, and the development of effective treatments is urgently needed. Recent phase III clinical studies have demonstrated that combining neoadjuvant chemotherapy with immune checkpoint inhibitors (ICI) can improve the response rate in early-stage triple-negative breast cancer (TNBC) patients. However, the addition of ICI can introduce unnecessary (and potentially permanent) toxicity and financial burden to non-responders. Currently, no biomarkers are available to identify individuals who require the addition of ICI to achieve pathologic complete response, a positive prognostic marker after neoadjuvant therapy. Developing blood-based biomarkers representing a dynamic immunologic response could help select appropriate patients, improve clinical trial success, and expand treatment applicability. In this study, we aim to identify peripheral immunological features that predict chemoimmunotherapy response in breast cancer patients.

Methods Longitudinal buffy coat blood samples were collected from 40 patients (20 hormone receptor-positive breast cancer and 20 TNBC) enrolled in the I-SPY2 trial’s paclitaxel (control) arm and pembrolizumab + paclitaxel (pembro4) arm. The blood samples were obtained at pretherapy, during early treatment (paclitaxel ± pembrolizumab), pre-anthracycline, and pre-surgery. We performed RNA sequencing to identify transcriptomic signatures associated with chemoimmunotherapy response. CibersortX was applied to estimated peripheral blood immune cell composition.

Results TNBC patients who responded to chemoimmunotherapy exhibited significant upregulation of genes associated with immune response and interferon response compared to non-responders at baseline. These signatures remained upregulated during therapy. Additionally, responders experienced an expansion of early-activated CD8 T cells in the peripheral blood after chemoimmunotherapy. Conversely, chemoimmunotherapy responders with HR+ breast cancer generally showed lower expression of genes related to immune activation compared to non-responders, and they maintained a substantial proportion of naïve CD8 T cells in their peripheral blood. After their initial treatment, all patients received four cycles of anthracycline therapy, which led to a significant upregulation of immune response genes, regardless of treatment arms, breast cancer subtypes, or response status.

Conclusions Our findings highlight the significance of immune activation signatures and the abundance of naïve and early activated CD8 T cells in predicting chemoimmunotherapy response. Additionally, we observed that anthracycline treatment elicits a potent immune response, suggesting its potential as a pre-treatment or combination therapy with ICI to enhance anti-tumor immunity (similar observation also reported in TONIC trial). To further validate these biomarkers and explore chemoimmunotherapy resistance mechanism, we plan to sequence the buffy coat samples from over 150 patients, encompassing all four timepoints, in the I-SPY2 control and Pembro4 arms.