Validation of a genomic assay in early-stage HER2+ breast cancer (BC) treated with trastuzumab and pertuzumab (HP): a correlative analysis from PHERGain phase II trial

1 in 5 women diagnosed with breast cancer have HER2+ disease, meaning that their cancer has an overexpression of a protein called human epidermal growth factor receptor 2 (HER2) and is associated with aggressive tumor growth. Currently, HER2+ patients with early breast cancer, meaning the tumor has not spread beyond the breast, are treated with a combination of chemotherapy and therapies that specifically target the HER2 protein. However, patients' responses are variable, and it is difficult to assess if they are receiving the best treatment option. Therefore, there is a large unmet need to develop tools that can help predict the benefit of these targeted therapies as well as the risk of recurrence.

HER2DX is the first genomic tool for patients with HER2+ early-stage breast cancer. The test measures the expression level of 27 genes related to cancer and then combines the information with the clinical characteristics of tumor size and lymph node involvement. This personalized data is then processed by an algorithm that calculates two independent scores – one indicating the probability of a patient suffering a relapse (prognosis) after treatment with trastuzumab-based chemotherapy (HER2DX risk-score) and one giving the probability of response to trastuzumab-based chemotherapy (HER2DX pCR score).

HER2DX has already been found to be a useful tool but still needs further validation. To test the predictive power, samples from the PHERGain study were used to see if the HER2DX tool was able to correctly provide the same results that occurred in the study. Briefly, the PHERGain study was designed to investigate the feasibility of a chemotherapy-free treatment approach for patients with HER2+ early breast cancer through a trial design that allowed for a patient's treatment to be changed based on how they were responding. (*For a lay language summary of the design and the results of the PHERGain trial at ASCO 2023 – click here*)

292 samples (82% of the total number of participants in the PHERGain trial) from patients who participated in the PHERGain trial were used to validate the HER2DX assay. The goal was to test the association of HER2DX pCR-score (prediction) with real pathological complete responses (the absence of any residual cancer cells after treatment) in PHERGain as well as the HER2DX risk-score (prognosis) with the real invasive disease-free survival outcomes (percentage of participants who are alive and free of breast cancer or any other type of cancer).

In terms of the HER2DX pCR-score or the probability of responding to treatment, it was found to be significantly associated with pCRs achieved in PHERGain. The percentage of patients without any residual cancer cells were 50.4% in the pCR-high, 35.8% in the pCR-medium, and 23.2% on the pCR-low.

For the prognostic or HER2DX risk-score, it was found that patients categorized with a low-risk score had a numerically better 3-year invasive disease-free survival time compared to patients

that were categorized with a high-risk score. 8 of the 9 patients with metastatic disease in the PHERGain trial received a HER2DX score in the high-risk category.

The HER2DX tool was able to predict pCR following a pre-surgery treatment (with and without chemotherapy) and seemed to be able to identify patients with a higher likelihood of recurrence. This assay may help individualize HER2-targeted therapies for early stage HER2+ breast cancer.