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HER2-PET imaging to predict trastuzumab deruxtecan (T-DXd) efficacy in advanced breast cancer: The phase II PREDICT-HER trial

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Background

T-DXd has shown remarkable efficacy in HER2-positive, HER2-low, and HER2-ultralow breast cancer (BC). However, single-site biopsy IHC fails to represent whole-body lesion status or in vivo antibody-target binding. HER2-PET imaging provides a non-invasive and whole-body visualization of HER2 target availability. This technology holds significant potential to refine patient selection and more accurately predict the efficacy of T-DXd.

Methods

This single-arm phase II trial enrolled advanced BC pts scheduled to receive T-DXd. HR+HER2-low/zero pts must have progressed on prior CDK4/6 inhibitors. Participants underwent baseline ^{18}F-FDG PET/CT and HER2-PET/CT using ^{18}F- or ^{68}Ga-labeled affibody molecules within one month prior to T-DXd initiation. Based on HER2-PET visual assessment of active lesions, pts were categorized into “HER2-PET-positive” (presence of HER2-avid lesions) and “HER2-PET-negative” (mild or no HER2 radiotracer uptake). The primary objective was to evaluate whether the negative predictive value (NPV) of HER2-PET-negative status for objective response was ≥85%. Correlations between normalized HER2 SUVmax and T-DXd response were also analyzed.

Results

By April 2026, 89 pts were enrolled (HER2-positive: 27; HER2-low: 54; IHC 0: 8) with a median of 1 prior line of anti-HER2 therapy or chemotherapy. mPFS was significantly longer in the HER2-PET-positive group vs. the HER2-PET-negative group (n=72 vs. n=17; 13.6 vs. 5.1 mo; multivariable-adjusted HR: 0.11, 95% CI: 0.05–0.26). Among 79 pts with measurable target lesions, the NPV of HER2-PET-negative status for T-DXd response was 88.2% (15/17), reaching 100% (10/10) in HER2-low/zero pts. The positive predictive value of HER2-PET-positive status in HER2-positive pts was 93.8% (15/16). Normalized HER2 SUVmax was higher in responders vs. non-responders (8.1 vs. 3.9, $P < 0.001$).

Conclusions

The initial results met the primary endpoint. HER2-PET redefines whole-body HER2 status in advanced BC. High NPV and striking PFS differences indicate that HER2-PET accurately identifies non-responders and could spare PET-negative pts from futile T-DXd. Integrating HER2-PET with IHC will optimize patient selection, particularly in HER2-low/zero BC.

Legal entity responsible for the study

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Disclosure

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