Artificial intelligence analysis of advanced breast cancer patients from phase I trial of Trastuzumab Deruxtecan: HER2 and histopathology features as predictors of clinical benefit

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Background

- Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) testing, and the corresponding ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines, are routinely used to identify breast cancer patients that benefit from HER2-targeting therapies [1].
  - These tests, however, are not optimized for identifying patients who might be eligible for novel HER2 targeted antibody-drug conjugates (ADC).
- Trastuzumab deruxtecan (T-DXd) [2], a novel HER2-target antibody-drug conjugate (ADC), demonstrated clinical benefit in HER2-positive (IHC 3+, IHC 2+/ISH+) and a portion of HER2-negative/HER2low (IHC 2+/ISH-, IHC 1+) advanced stage breast cancer patients as part of the DS8201-A-J101 phase 1, two-part, multicenter, non-randomized, open-label trial.
  - Patients were enrolled based on local HER2 results and HER2 status was centrally confirmed based on an FDA approved test using 2013 ASCO/CAP guidelines. This HER2 Low population is traditionally categorized as HER2-negative according to ASCO/CAP guidelines.
- To develop a more quantitative and reproducible assay for HER2 positivity, and clinical benefit for T-DXd, we applied a machine learning (ML) approach trained on expertly labeled breast cancer (BC) histopathology images.
  - ML approach enables capture of orthogonal histopathologic features such as quantification of tumor infiltrating immune cells and their spatial localization, which may further inform the likelihood of patient response to T-DXd.
- Here we evaluate the utility of our approach versus manual scoring for predicting patient outcomes and investigate associations between our interpretable ML derived features and clinical parameters including manual HER2 scores.

Methods

- Whole slide digital HER2 and H&E images were available for analysis from 154 enrolled BC patients from the DS8201-A-J101 trial.
  - Samples were digitized using the Aperio AT2 scanner and uploaded to the PathAI research platform (PathAI; Boston, MA; not intended for diagnostic purposes).
- 87 board certified pathologists were selected to annotate tissue regions and cellular foci on the PathAI research platform yielding 91,247 annotations **[Table 1].**
- ML models based on convolutional neural networks were trained to recognize partial and complete HER2 membranous positivity in BC cells, immune cells, and tissue compartments within the HER2 stained BC samples.
  - Once trained, models were evaluated on a held out set of BC samples.
- We generated human interpretable features by aggregating predictions across the entire whole slide image, producing 1,719 patient-level features.
  - ML derived patient-level features were clustered and selected, with false discovery rate control, for predicting patient outcomes and HER2 status **[Table 2].**
  - Thresholds for feature-based patient selection were identified using 10-fold cross validation optimizing for hazard ratio (HR) between patients with feature values above and below the threshold.

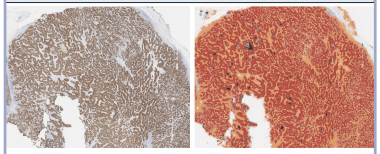
Results

- Images and clinical data were available from 149 of the BC patients treated with T-DXd for inclusion in this study.

Table 1. Summary of Pathologist Annotations

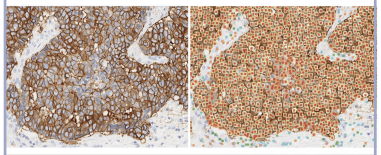
Region Type	Count	Cell Type	Count
Artifact	1520	Cancer Cells	49915
Pre-invasive lesions	583	Fibroblast	5613
Cancer Stroma	4494	Lymphocytes	6961
Cancer Epithelium	10130	Macrophages	1545
Necrosis	691	Plasma cell	262
Normal Tissue	2906	Other/Non-cell	6627

Figure 1: Example Predictions of Breast Tissue Segmentation Algorithms



Left Image: HER2 Stained BC Sample; Right Image: Imposed ML predictions. Red indicates invasive BC epithelium, orange indicates cancer stroma, black indicates necrosis and no color indicates non-tumor and background regions

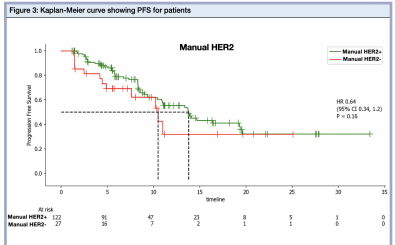
Figure 2: Example Predictions of Cell Prediction Algorithms



Left Image: HER2 Stained BC Sample; Right Image: Imposed ML predictions. Red indicates invasive BC cell (yellow border indicates complete HER2 membranous positivity, orange border indicates partial HER2 membranous positivity), orange indicates fibroblast, green indicates lymphocyte and aqua indicates macrophage

- Manual HER2 scoring, selecting 122 patients (81.8%), was not found to be significantly associated with PFS (HR 0.64 [95% CI 0.339, 1.198], p=0.162), as well as not significantly associated with ORR (52.5% vs. 40.7% (p=0.29)) **[Figure 3]**

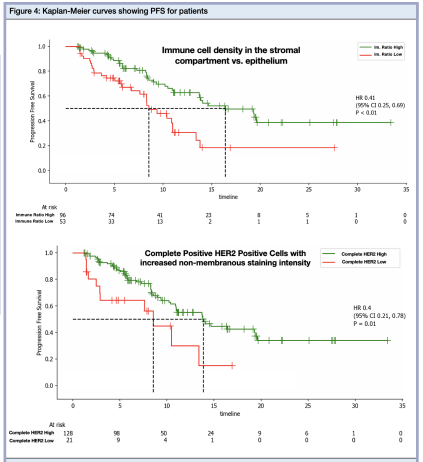
Figure 3: Kaplan-Meier curve showing PFS for patients



Kaplan-Meier curves showing PFS for patients that were high for Manual HER2 scoring

- Quantitative measurements of immune cell (macrophage and lymphocyte) density ratio in the tumor stroma vs. the tumor epithelium, selecting 96 patients (64.4%), was found to be significantly associated with PFS (HR 0.415 [95% CI 0.25, 0.687], p<0.001) and ORR (57.3% vs. 37.7% (p=0.027)) **[Figure 4]**
- Furthermore, a ML generated feature measuring complete membranous HER2 positive BC cells with increased Peri-nuclear/cytoplasmic HER2 staining, selecting 128 patients (85.9%), was found to be significantly associated with PFS (HR 0.404 [95% CI 0.21, 0.78], p=0.007) and ORR (55% vs. 24% (p=0.009)) **[Figure 4]**

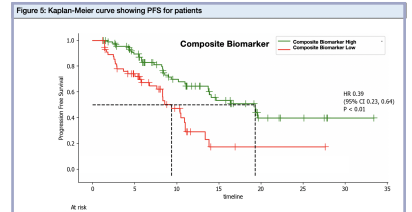
Figure 4: Kaplan-Meier curves showing PFS for patients



Kaplan-Meier curves showing PFS for patients that were high for selected features of immune cell density in the stromal compartment vs. epithelium (above) and complete positive HER2 cells with increased non-membranous staining intensity (below).

- A composite biomarker utilizing both significant features, the immune cell density ratio in the tumor stroma vs. the tumor epithelium and the feature measuring complete membranous peri-nuclear/cytoplasmic HER2 staining, selecting 92 patients (61.7%), was found to be significantly associated with PFS (HR 0.389 [95% CI 0.225, 0.644], p<0.001) and ORR (59% vs. 37%), p=0.011) **[Figure 5]**

Figure 5: Kaplan-Meier curve showing PFS for patients



Kaplan-Meier curves showing PFS for patients that were high for a selected feature combining the immune cell density in the stromal compartment vs. epithelium and complete positive HER2 cells with increased non-membranous staining intensity.

Table 2. Results of Association Between PathAI Derived Features, Manual HER2 Scoring and Patient Survival and Response

	Manual HER2	Complete Positive Cells	Immune Infiltration	Composite Biomarker
% Positive Patients	81.9%	85.9%	64.4%	61.70%
% Negative Patients	18.1%	14.1%	35.6%	38.30%
HR (95% CI) p-value	0.637 (0.339-1.198) p=0.162	0.404 (0.209-0.78) p=0.007	0.415 (0.25-0.687) p<0.001	0.389 (0.235-0.644) p<0.001
ORR (All) (95% CI)	50.3% (42%-58.6%)	50.3% (42%-58.6%)	50.3% (42%-58.6%)	50.3% (42%-58.6%)
ORR (Selected) (95% CI)	52.5% (43.2%-61.6%)	54.7% (45.7%-63.5%)	57.3% (46.8%-67.3%)	58.7% (47.9%-68.9%)
ORR (Unselected) (95% CI)	40.7% (22.4%-61.2%)	23.8% (8.2%-47.2%)	37.7% (24.8%-52.1%)	36.8% (24.4%-50.7%)
ORR (Selected vs. Unselected) p-value	p=0.295	p=0.009	p=0.027	p=0.011

Survival results summary table. Manual HER2 IHC scoring, according to the ASCO/CAP guidelines (1st column), HER2 complete membranous cancer cells with increased non-membranous staining binary feature (2nd column), High immune density in stroma vs. epithelium ratio feature (3rd column), Composite PathAI biomarker selects patients positive for both the immune density stroma/epi ratio feature and complete membranous with increased non-membranous features (4th column).

Conclusions

- ML models accurately identify tissue compartments, immune cells, and HER2 positivity in BC cells within the T-DXd patient sample cohort.
- ML generated features measuring complete membranous HER2 positive BC cells with increased peri-nuclear/cytoplasmic HER2 staining selects more patients (85.9% vs 81.8%), while maintaining a comparable HR (0.404 vs 0.637) and ORR (54.7% vs 52.5%) to manual HER2 scoring.
- These results highlight the potential of ML models to select patients for anti-HER2 therapy above and beyond conventional HER2 scoring in an automated fashion.

References

1. Wolff, A et al. Arch Pathol Lab Med. 2018; 142:1364–1382
2. Tamura, K et al. Lancet Oncol. 2019 Jun;20(6):816-826

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Disclosures

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