Identification of poor responders to trastuzumab-deruxtecan with a multi-modal HER2 status predictor

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Published Abstract Number: 2502

INTRODUCTION

Trastuzumab deruxtecan (TDXD) is approved for HER2-low or HER2-positive metastatic breast cancer. HER2 status is assessed through HER2 IHC and FISH assays, and has been correlated to RNA expression.

This study aimed to:

1) Create a molecular model that combines RNA with DNA to predict HER2 status from IHC+FISH. This model will objectively report a score for each patient.

2) Evaluate if the model score can be used to stratify patient response to TDXD.

METHODS

Training (n=1275) and test (n=397) sets of breast cancer samples from the Tempus Database with reported HER2 status, xT DNA and xR RNA expression profiling.

Molecular profiling with Tempus NGS assays

xR Whole-transcriptome RNA + xT 648-gene targeted DNA

A 12-gene random forest model was trained on RNA expression and DNA copy number to predict HER2-positivity. Stepwise gene selection on RNA and DNA features when predicting HER2-positivity using a random forest model.

To assess the relationship between model score and response to TDXD, a discovery cohort of 284 patients was curated. It contained patients who received TDXD after RNA and DNA collection and had at least a 30-day follow-up.

The model was applied to the TDXD cohort, and the patient cohort was partitioned into three equal-sized groups (33 1/3%), according to model score. The three groups were low-score, intermediate-score, and high-score.

Overall survival from time of TDXD administration was assessed for each group. Significance was assessed by a log-rank test comparing the low-risk group with the high-risk group.

ACKNOWLEDGEMENTS

We thank Matthew Kase from the Tempus Scientific Communications team for poster development.

SUMMARY

- A multimodal RNA+DNA model outperforms a HER2 RNA-only model in predicting HER2 positivity as assessed by IHC+FISH.
- Low model scores were associated with HER2-negativity and high model scores were associated with HER2-positivity.
- In a real-world cohort of patients treated with TDXD, the predicted HER2 score was negatively correlated with OS (concordance index = 0.68).
- Partitioning the TDXD cohort into thirds according to model score (low, intermediate, high) found that patients that were low scoring had significantly worse OS compared to high scoring patients (log rank p < 1e-3).

RESULTS

HER2 status in the training, test, and discovery cohorts

HER2 status/ Dataset	Train (n=1275)	Test (n=397)	TDXD cohort (n=284)
negative	361 (28%)	114 (29%)	2 (1%)
low	774 (61%)	237 (60%)	33 (12%)
positive	140 (11%)	46 (12%)	22 (8%)
unknown	0	0	227 (80%)

Figure 1. Distribution of HER2 statuses in the training, test, and discovery (TDXD) cohort. The TDXD cohort has a higher proportion of missingness for HER2 status because the other 2 datasets were chosen for the HER2 model training and evaluation and there were fewer TDXD samples.

Multimodal DNA+RNA predictor outperforms RNA-only univariate HER2 predictor

HER2 RNA-only model

True / Predicted	Non-positive	Positive
Non-positive	**312**	6
Positive	7	**35**

Statistic	Value	SE
PPA	**83.22%**	0.181%
NPA	**98.10%**	0.024%
PPV	**85.26%**	0.171%
Indeterminate range	**9.34%**	.045%

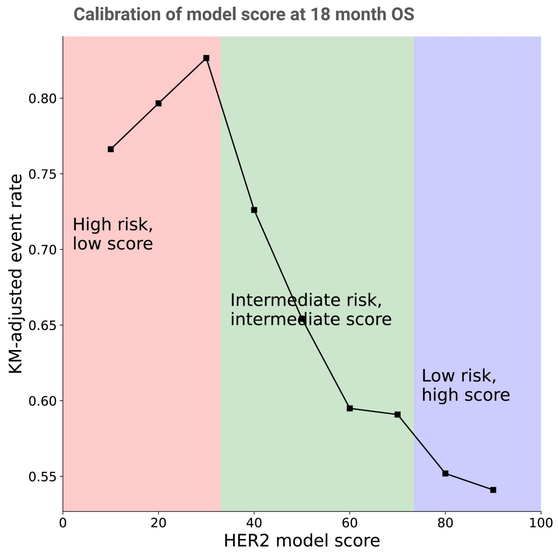
RNA + DNA model

True / Predicted	Non-positive	Negative
Non-positive	**300**	5
Positive	3	**27**

Statistic	Value	SE
PPA	**91.07%**	0.158%
NPA	**99.02%**	0.018%
PPV	**91.11%**	0.153%
Indeterminate range	**14.11%**	.057%

Figure 2. When comparing the RNA-only HER2 gene TPM model and the 12-gene RNA and DNA model performance, the combined model outperforms particularly on PPA and PPV. HER2-positive is defined as HER2 IHC 3+, or IHC 2+ FISH+

Predicted HER2 score was positively correlated with OS TDXD-treated patients



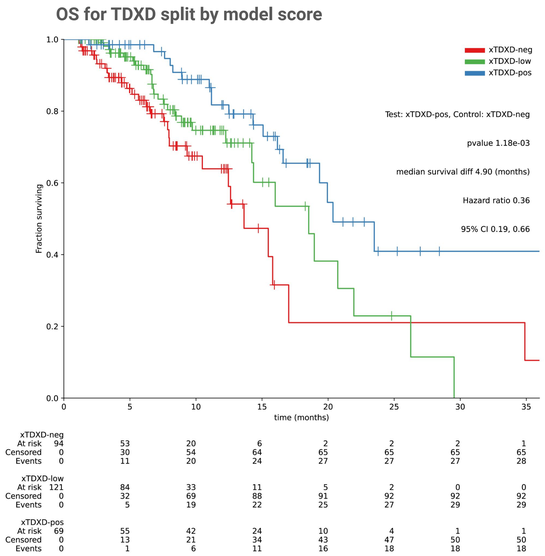


Figure 3. The relationship between model score and survival on TDXD, as measured by OS event rate at 18 months after TDXD medication start date. Low model scores associate with high-risk, whereas, high model scores associate with low-risk. Score-groups determined by partitioning the population to thirds according to their score.

C-index: 0.64

Figure 4. Partitioning the TDXD cohort to three equal sized sub-cohorts (33.33%) ordered by model score: low, intermediate, and high. Median OS in months for groups was: low 13.6, intermediate 18.5, and high 20.4. High-group patients had significantly better OS on TDXD compared to the low-group (HR = 0.39, log-rank p-value < 0.002).

DISCUSSION

Creating a multimodal model to predict HER2 status has resulted in a model that stratified TDXD patients by OS in real-world data. Since sample collection for this cohort was before administration of TDXD, these results imply that patients that are expected to do poorly on TDXD may be identified prior to TDXD administration. Further investigation into these tumors biology may shed light on sensitivity to other potential therapies.

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