Targeting clinically advanced breast cancer with conjugated and unconjugated HER2 antibodies: Does copy number matter?

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ABSTRACT

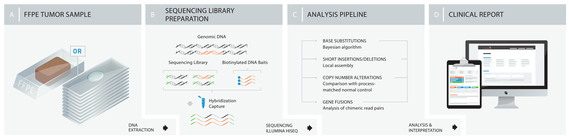
Background
HER2-targeted therapy is broadly used in advanced breast cancer (aBC). For HER2+ aBC (HER2 IHC 3+ or 2+/ISH+), 1L standard of care includes unconjugated HER2 antibodies trastuzumab and pertuzumab (HP) in combination with chemotherapy. In the 2L+ setting, antibody drug conjugate trastuzumab deruxtecan (T-DXd) can be used for HER2 low (IHC 1+, 2+/ISH-) patients with significant benefit seen in DESTINY Breast 04 relative to physicians' choice chemotherapy. For some targeted therapies, including MET inhibitor capmatinib, the magnitude of genomic copy number (CN) gains predict benefit. Here, we examined a real-world cohort of aBC patients (pts) treated with HER2 antibody therapies to determine if *ERBB2* genomic CN ratio predicts outcomes.

Results
121 pts with HER2+ aBC were treated with HP + chemotherapy in 1L and received genomic profiling before start of 2L. *ERBB2* CN ratio was generally high (median *ERBB2* CN ratio of 10; IQR 2.8-17.8). Pts with a *ERBB2* CN ratio of >5 (equivalent to CN 10 in a diploid tumor) had significantly better Real-world time to treatment discontinuation (rwTTD) (median 8.4 v 5.3 mo, HR = 0.55, 95% CI 0.36-0.84, p = 0.006), and rwOS (median 76 v 31mo, HR = 0.33 95% CI 0.18-0.61, p <0.001) than pts with a *ERBB2* CN ratio of ≤5, and comparable trends were observed for real-world progression free survival (rwPFS)(median 13v 9mo, HR = 0.81 (95% CI 0.52-1.26), p = 0.35). Similar benefit was seen for pts with a *ERBB2* CN ratio of 5-10, 10-15, 15-20, and 20+ relative to *ERBB2* CN ratio ≤5.

For 95 pts with HER2 low BC treated with T-DXd in the 2L or 3L setting, *ERBB2* CN ratio was generally low (median ratio of 1, IQR 1-1) with a maximum *ERBB2* CN ratio of 2.5 in the cohort. Based on exploratory analysis, outcomes were similar across *ERBB2* CN ratio, with the exception of pts with a *ERBB2* CN ratio of ≤0.5 (11/95; 12%) who had significantly worse rwPFS (median 2.5 v 6.1 mo, HR = 0.37, 95% CI 0.17-0.79 p = 0.01) and OS (median 6.5 v 25.2 mo; HR =0.32, 95% CI 0.14-0.75; p=0.008) than pts with a HER2 CN ratio of >0.5, with similar trends for rwTTD (median 1.6 v 4.8 mo, HR = 0.52, 95% CI 0.26-1.06 p = 0.07).

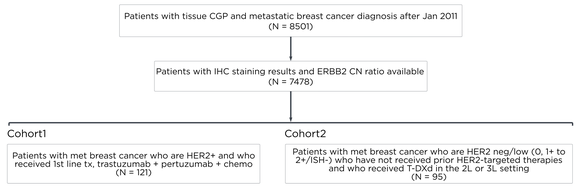
MATERIALS AND METHODS

Comprehensive genomic profiling workflow



ClinicoGenomic Database

- This study used the US nationwide de-identified Flatiron Health (FH) and Foundation Medicine Inc. (FMI) clinico-genomic database (CGDB) including patient-level structured and unstructured retrospective longitudinal clinical and genomic data from approximately 280 cancer clinics (approximately 800 care sites) in the United States and included patients who underwent tissue next generation sequencing (NGS)-based comprehensive genomic profiling (CGP) (FoundationOne®/FoundationOne®CDx) from 2014-2023.
- *ERBB2* CN ratio was defined as ratio of modeled absolute CN to specimen ploidy.
- *ERBB2* amplifications were defined as modeled CN >= ploidy +3



RESULTS

Figure 1. Patient Characteristics

	Cohort 1		p value	Cohort 2		p value
ERBB2 Amp ratio	<=5	>5		<=0.5	>0.5	
Number of patients	(N=38)	(N=83)		(N=11)	(N=84)	
Age in years, median (range)	64 (53, 72)	55 (46, 66)	0.0254	55 (48, 65)	59 (52, 69)	0.463
Sex			0.232			1
- Female	36 (94.7%)	82 (98.8%)		11 (100.0%)	84 (100.0%)	
- Male	2 (5.3%)	1 (1.2%)				
Race			0.906			0.331
- White	24 (63.2%)	57 (68.7%)		4 (36.4%)	49 (58.3%)	
- Asian	0 (0.0%)	1 (1.2%)		0 (0.0%)	1 (1.2%)	
- Black or African American	6 (15.8%)	10 (12.0%)		2 (18.2%)	8 (9.5%)	
- Other or multiple races	6 (15.8%)	10 (12.0%)		0 (0.0%)	6 (7.1%)	
- Unknown race	2 (5.3%)	5 (6.0%)		5 (45.5%)	20 (23.8%)	
Stage			0.107			0.0647
- Stage I	6 (15.8%)	4 (4.8%)		0 (0.0%)	10 (11.9%)	
- Stage II	11 (28.9%)	14 (16.9%)		4 (36.4%)	24 (28.6%)	
- Stage III	4 (10.5%)	11 (13.3%)		7 (63.6%)	22 (26.2%)	
- Stage IV	16 (42.1%)	50 (60.2%)		0 (0.0%)	17 (20.2%)	
- Unknown/not documented	1 (2.6%)	4 (4.8%)		0 (0.0%)	11 (13.1%)	
ER status			0.0793			0.403
- Negative	13 (34.2%)	46 (55.4%)		6 (54.5%)	35 (41.7%)	
- Low Positive	4 (10.5%)	3 (3.6%)		1 (9.1%)	2 (2.4%)	
- Positive	18 (47.4%)	26 (31.3%)		4 (36.4%)	41 (48.8%)	
- Positive NOS	3 (7.9%)	8 (9.6%)		0 (0.0%)	6 (7.1%)	
ECOG			0.885			0.002
- 0	21 (55.3%)	39 (47.0%)		2 (18.2%)	33 (39.8%)	
- 1	12 (31.6%)	27 (32.5%)		3 (27.3%)	36 (43.4%)	
- 2	2 (5.3%)	6 (7.2%)		4 (36.4%)	7 (8.4%)	
- 3	1 (2.6%)	2 (2.4%)		2 (18.2%)	0 (0.0%)	
- Unknown	2 (5.3%)	9 (10.8%)		0 (0.0%)	7 (8.4%)	

Figure 2. High *ERBB2* CN ratio is associated with with HER2 IHC 3+ staining. The top plot shows the distribution of HER2 IHC status within each *ERBB2* CN ratio bin. The bottom plot shows the distribution of *ERBB2* CN ratio in each HER2 IHC staining group (0, 1+, 2+, 3+).

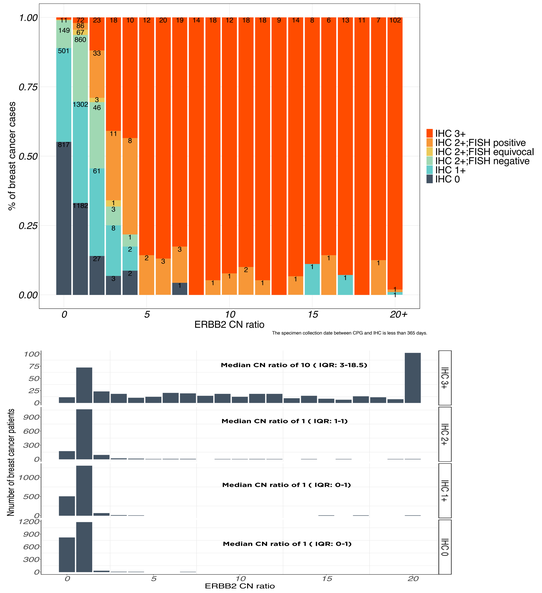


Figure 3. *ERBB2* amplification is associated with benefit on 1L trastuzumab/pertuzumab + chemo in 1L mHER2+ breast cancer. rwTTD, rwPFS and rwOS were examined for patients who were HER2+ by IHC with either a reported amplification in *ERBB2* or without an *ERBB2* amplification reported based on genomic profiling.

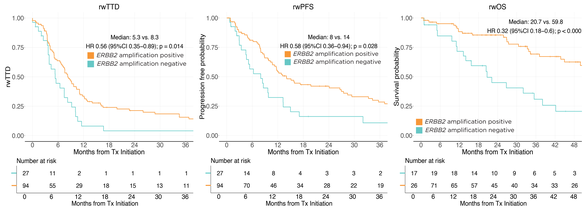


Figure 4. *ERBB2* CN ratio of 5 is associated with longer response to 1L trastuzumab/pertuzumab + chemo in 1L mHER2+ breast cancer. rwTTD, rwPFS and rwOS was examined for patients with *ERBB2* CN ratio of >5 v ≤5 (left plots). rwTTD and rwOS were similar for patients with a *ERBB2* CN ratio of <2.5 and 2.5-5. Patients with CN ratio of ≥5 had similar benefit on 1L t/p + chemo regardless of CN ratio bucket (right plots)

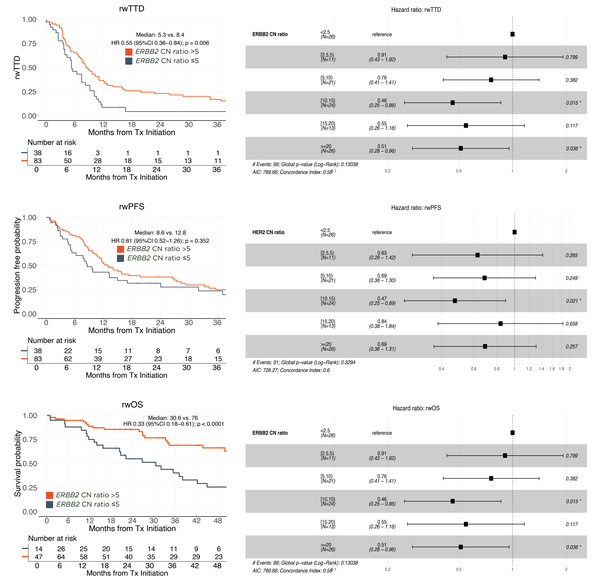


Figure 5. *ERBB2* CN ratio of ≤0.5 is associated with poor outcome to TDXd in 2L+ HER2-low metastatic breast cancer. rwTTD, rwPFS and rwOS was examined for patients with *ERBB2* CN ratio of >0.5 v ≤0.5. The *ERBB2* CN ratio of 0.5 is based on exploratory analysis. Two patients could not access rwPFS, so they were removed from the analysis

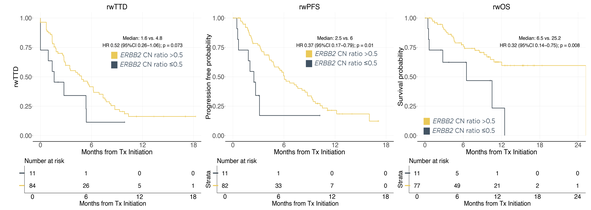
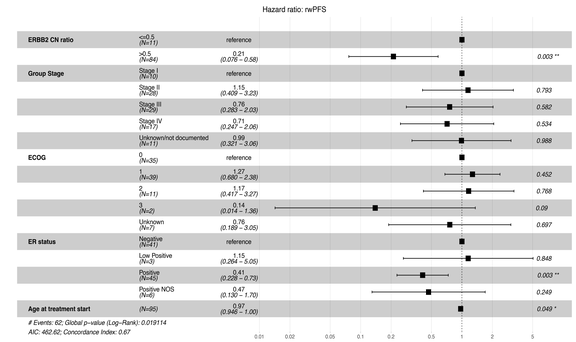


Figure 6. *ERBB2* CN ratio of ≤0.5 is associated with poor outcomes on TDXd in 2L+ HER2-low metastatic breast cancer even after multivariate analysis. Due to imbalances in arms, we performed a multivariate analysis including stage, ECOG, ER status and age at treatment start. rwPFS (shown below) demonstrated significant associations between an ERBB2 CN ratio >0.5 and with comparable trends observed for rwTTD (aHR= 0.71 (95% CI 0.28-1.7), p = 0.45) and rwOS (aHR= 0.53 (95% CI 0.17-1.64), p = 0.27).



CONCLUSIONS

- *ERBB2* CN ratio is significantly associated with clinical outcomes.
- For unconjugated antibodies, pts with a *ERBB2* CN ratio of ≤5 had significantly shorter rwTTD, rwPFS and OS. Future work should explore whether these pts may benefit from therapy escalation and/or increased surveillance.
- For T-DXd, pts with a hemizygous or deep deletion in *ERBB2* (*ERBB2* CN ratio ≤ 0.5) had significantly worse outcomes, consistent with partial or complete target loss.
- These results suggest that *ERBB2* CN ratio can provide additional predictive information to treatment decisions that are currently defined by HER2 IHC status.
- *ERBB2* CN ratio strongly correlates with IHC scores, though there isn't a 1:1 mapping between scores.